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ON THE PRESENT STATUS OF THERAPY AND ITS FUTURE.*

By Lewellys F. Barker, M. B., *Tor.*,

Associate Professor of Pathology, Johns Hopkins University.

The only means we have of judging what the future has in store is to review the history of the past and to view accurately the present tendency or drift. The history of therapy is the history of medicine, for medicine began with therapy. It is not my purpose in the time allotted to me to undertake a recital of this history; I shall have to be content simply with an enumeration of epochs and perhaps a hint at the periods of progress.

Historians are gradually collecting for us the data concerning the earliest therapeutic efforts. The history of the earliest medicine shows of what a jumble these efforts consisted. With the dawn of intelligence the sympathy which was gradually evolved through the sense of pain led the primitive man to attempt to relieve the pain of his fellows. You recall the lines of a literary medical man:

> "The hunt is o'er; the stone-armed spears have won;
> Dead on the hillside lies the mastodon.
> Unmoved the warriors their wounded leave;
> The world is young and has not learned to grieve.
> But one, a gentler sharer of the fray,
> Waits in the twilight of the western day,
> Where 'neath his gaze a cave-man, hairy, grim,
> Groans out the anguish of his mangled limb.
> Caught in the net of thought the watcher kneels,
> With tender doubt the tortured member feels,
> And, first of men a healing thought to know,
> He finds his hand can check the life-blood's flow."

Disease is as old as man—it is only the knowledge of disease that is recent. In the fiercer physical struggle for existence which must have characterized the life of our primitive forefathers, external wounds and manglings, as well as physical injuries due to exposure to the weather, to extremes of cold and heat, must have been common. Crude surgical procedures evolved by herdsman or shepherd began to be applied to man. The diseases peculiar to the female sex were first treated by the wise old women who had lived through the mysteries of the life of that sex. Of the nature of disease in general and particular the ghost of a true idea did not exist. Obscure diseases were regarded as instances of demoniacal possession. Prayers, chants and sacrifices to healing gods were universal. Devils were exorcised chiefly through the medium of priests. The priestly art and that

*Address in medicine delivered before the Ontario Medical Association, Toronto, June 6th, 1900.

of the physician were often combined. In China, in India, in Chaldea, in Egypt, the development of early medicine followed the same fundamental principles, though each country manifested special peculiarities.

The medicine of the Greeks interests us as much as any. Philosophers all, with an intense longing for the good, the true and the beautiful, they have left behind them records which in many respects make modest even the reader of to-day. In Heraclitus, Democritus and Empedocles and, above all, in Hippocrates we meet with much that is practically good in modern medicine and philosophy, especially as concerns the individual life, the ideal development of the personality. Though infants in anatomy and physiology and almost entirely ignorant of the nature of specific diseases, the Greek physicians had accumulated an account of symptoms and conditions and a therapeutic armamentarium that surprises the modern who for the first time reads his Hippocrates. The treatment of fractures and dislocations, the trepanning of the skull, the tapping of the abdomen and chest, the mode of dealing with hernia show us how daring they were in surgical measures. Had they known how to control hæmorrhage, who can tell what operations these cool-headed Greeks might not have devised. They were far less happy in the more difficult field of internal medicine. Most of their ideas about internal diseases were wrong, but some of their descriptions of individual cases are magnificent. Concerning the therapy of internal diseases, Hippocrates had many sound principles, and described some good practice. He recognized the healing power of nature and urged his followers to aid and follow nature—"quo natura vergit, eo tendere oportet." In Hippocrates can be found the tenets of many of the famous schools which have followed him. The principle of "contraria contrariis" and that of "similia similibus" are both in his pages, but wiser than some who came after him he limited himself to neither. "According to its kind and the circumstances underlying it, a case must sometimes be treated by agents acting unlike the disease, sometimes, on the other hand, the treatment must be undertaken by agents acting similar to the disease. The reason for this lies in the weakness of the human organism." Perhaps the strongest part of the therapy of that day was in the emphasis laid upon diet, gymnastics, bathing and mode of life in general. Who but has read and appreciated the Charmides of Plato, that exquisite dialogue in which the principles of Greek temperance are embodied. For a long time after Hippocrates this personal hygiene was accentuated. The visits of young men to the temples of Æsculapius, there to be instructed as to how to live, were long continued. Walter Pater's appreciation of a visit of this sort described in Marius the Epicurean will be recalled by many of you.

In Galen's time theory and gross empiricism reigned supreme. The idea of the four elements, heat, cold, dryness and moisture influenced the giving of drugs. These elements in a sense corresponded to the four cardinal juices of the human body, blood, mucus, yellow bile and black bile. The therapeutic ideas of Galen, like his medical ideas in general, dominated medicine for a thousand years.

With the advent of Vesalius and the development of human anatomy one might have hoped for rapid improvement in therapy, but this improvement was not immediately forthcoming. Even Harvey's discovery of the circulation of the blood and Malpighi's studies of physiology and pathology were not immediately fruitful in a therapeutic way. Paracelsus alone stands out as a reformer in internal medicine and therapeutic effort. He bravely opposed the authority of Galen, recognized the fallacy of trusting to knowledge obtained from books and relied rather upon personal observation and experience. Analysis shows, however, that even Paracelsus did but little to advance the actual knowledge of therapy.

About this time there was a wide-spread awakening in all the natural sciences. Descriptive natural science and systemization ruled the thought of the day. During the period which followed a series of medical systems developed, based upon one-sided theories and badly based generalizations; Haller's doctrine of irritability, Brown's doctrine of stimuli, Hahnemann's homoeopathy, Gall's phrenology, along with many other schools came at this period to their development.

Real progress in therapy dates from the time when natural science became an exact study. Rigidly accurate observation followed by mature reflection has led to experimentation. Medicine of this sort is only a century old. It was almost synchronous with the widening of chemical discovery and of the working out by physicists of the principles which underlie many natural phenomena which up to the time had been entirely obscure, that microscopic studies began to be prosecuted seriously. Histology developed with Bichat; the cell doctrine with Schleiden and Schwann, pupils of the celebrated Johannes Müller. The French and the Germans became enthusiastic for pathological anatomy. Rokitansky counted his autopsies by thousands. The older physicians like Sydenham and Bœrhaave, found worthy successors in Louis, Schönlein, Traube, and Wunderlich.

Virchow's cellular pathology established an entirely new view-point whence disease-processes could be observed. Charles Darwin's work on the "Origin of Species," Herbert Spencer's philosophy and Huxley's researches in comparative anatomy stimulated investigators in all sciences to examine into the evolution of phenomena, to consider the order of events in organic processes. Enormous strides continued to be made in physics and chemistry, and the new facts discovered in these branches permitted of the development of physiology by Ernst Brücke, Carl Ludwig, Emil Du Bois Reymond, Helmholtz and Claude Bernard. Caspar Fr. Wolff, Karl von Baer, Balfour, and His unravelled the mysteries of embryonic development. Improvements in the microscope and in microscopic technique led to a deeper penetration into the mysteries of histology and microscopic anatomy, normal and abnormal, than the most enthusiastic could have hoped for a few years earlier. New instruments of all sorts were

devised. Auenbrugger's percussion and Laennec's auscultation revolutionized physical diagnosis. The ophthalmoscope, the laryngoscope and the speculum, had much to do with the establishment of the specialties of ophthalmology, laryngology and gynæcology.

In the fight against infectious diseases a great victory had been won in the discovery of vaccination by Edward Jenner. Later on Henle's ingenious speculations concerning the nature of contagious diseases set many great minds in motion. With Pasteur and Koch came illumination. The infectious agent in the majority of infectious diseases is now known, can be cultivated in pure culture and can be utilized in animal experiment.

Physiological and pathological chemistry have been unveiling the mysteries of the fluids and solids of the body; pharmacology and toxicology are investigating the influences of drugs and poisons upon these. The application of Lister's happy idea with regard to wound infection, aided by the American-born boon of anæsthesia and a bloodless technique, totally changed the aspects of surgery. Wound infection, if not entirely an event of the past, has been enormously reduced. The holiest places of the body are to-day invaded by the surgeon's knife; the abdomen, the thorax, the joint cavities and even the brain are frequently and fearlessly explored. The heart, the last organ of man to be made accessible to surgical treatment, can now be sutured with success.

But more time must not be spent in glancing at the past; it is necessary at once to look at the present and to divine, if it be possible, whither we are being led.

As a result of development along so many diverging lines the study of modern medicine is concerned with a field so wide that he who glances over it, cannot fail to be appalled by its magnitude. No single intelligence can in these days be familiar with the details of growth in all its parts; no single individual can hope to work efficiently in more than one or two of its subdivisions. The complexity of the work demands a division of labor, and most is gained from the efforts of men who, familiar with the general trend of progress in the whole field, concentrate their activities upon some one corner of it. Individual workers in the special medical sciences are pushing their investigations at the moment with unwonted zeal. Anatomists are ever devising new technical methods; the cells formerly believed to be very simple "elements" are found to be highly complex organisms; parts of the body as, for example, the nervous system, are having their true cellular nature for the first time revealed; the structural basis of the intrinsic mechanisms of individual cells is in process of demonstration; the relations of the basis in one cell to that in other cells are being found out. Physiology, so long interested in the hydraulic principles of the circulatory apparatus and the muscle-nerve preparation, is being diverted into new channels of research, utilizing in its experiments the newly discovered principles underlying chemical and physical phenomena. The oxygenating and reducing processes which occur in the body, the various stages of anabolic and catabolic metabolism, the phenomena of secretion and excretion, the interrelations of the various bodily activities, the functions of the different neural complexes, the mechanisms of defence and adaptation—these are some of the subjects with which physiologists are now busying themselves.

In pathological anatomy and physiology just as strenuous efforts are being made as in the other fundamental departments. Our ideas concerning inflammation have been so much modified that we are advised by some of the ablest pathologists to give up the term altogether. The nature of inflammatory exudates is still under discussion; what elements are of hæmic and what of local origin are disputed; the great cleft between the acute inflammations and the chronic processes associated with production of new connective tissue is still unsatisfactorily bridged. The ætiology of tumors, as yet unsolved, stimulates the embryologist on the one hand and the parasitologist on the other to renewed exertion. New tumors are being discovered; old ones are being regrouped; finer and finer distinctions between benignancy and malignancy are being drawn with results eminently satisfactory for the practical surgeon.

The therapeutic hopelessness that pathological anatomy inspires is more than compensated for by the faith in the future of therapy and prophylaxis directly derivable from a consideration of the teachings of pathogenesis. As pathological processes are traced further and further back to the earliest stages when function begins its deviation from the normal and the causes underlying those deviations gradually become recognizable the means of prevention and the indications for treatment become obvious.

Bacteriology appears to have done for us the greatest work of which it is directly capable; further advances in a similar direction promise to be made rather through the aid of chemistry and physics. The study of protozoan invasions is yet in its infancy and may have surprises in store for us. One cannot help but feel that we are on the brink of the discovery of the infectious agent in syphilis and the infectious fevers, but who can prophesy what the nature of the agent will be—animal, vegetable or less highly organized "ferment."

We have some reason to be proud of the present status of public hygiene. There never was a time when the general public was more industriously educated concerning the importance of hygienic measures than at present—never a time when the laity was more thoroughly exercised over this topic. Sanitary associations are innumerable; public health departments are everywhere demanded. Meat, milk and vegetables are inspected; impurities in food and drink are more and more excluded through the vigilance of the law. Contagious diseases are diagnosed early and isolated by city officials. Governmental sanitaria are in sight. Quarantine and disinfectant measures are more rigidly and fortunately more intelligently employed than ever before. Great epidemics are being choked at their starting places, the only mode in which they can satisfactorily be combatted. A fire can be extinguished by a fire department in its incipient stage—once well

under way it is beyond the control of human interference. There is good prospect that ere long the world will be through with those tremendous outbreaks of contagious disease of bacterial origin which from time to time have so devastatingly swept over both Western and Eastern civilizations. Thanks largely to Anglo-Saxon enterprise the back yards of the world in which the embers of epidemics smoulder are being rapidly cleaned up; this together with the rendering ever more infection-proof of the materials to which the flame of infection spreads bids fair to make the whole subject if not entirely, at least largely, a matter of history.

The present position of personal hygiene is a subject upon which we have less reason to congratulate ourselves. In principle we know much, in practice we do but little. Concerning climate, fresh air, diet, clothing, bathing, work, rest and recreation there is perhaps less dearth of information than negligence and inattention in performance. We behave hygienically when we are forced to do so, but not as a well planned order of life. Above all on this continent we have as yet to learn how to live and the problem here is less simple than elsewhere, for life here, especially in the great centres, is life at its most complex. Nowhere else is the strain so great—nowhere else does it so rapidly increase in tension. It must be a nervous system other than that which has been and that which is that will stand it. That nervous system may be now evolving, but in the meantime the unfit are succumbing in numbers ever more alarming. Moderation in all things and elimination of the non-essential from our lives would do much to tide us as a race over the transition period.

Perhaps the most significant movement at present observable in medicine is the beginning of the application of the newer ideas of physics and chemistry to the solution of biological questions. One has ever to be on his guard lest he expect too much from the introduction of new methods of approaching problems, but in this instance the principles underlying are so fundamentally important and have already worked such marvelous transformations in the mode of thought and activity of chemists that we are justified in expressing great hope for the future in their use by medical investigators. The doctrines of van't Hoff and Arrhenius are pregnant with great possibilities. van't Hoff's brilliant generalizations with regard to the behavior of solutions are found to hold good by a whole series of workers—the laws of osmotic pressure appear to be strictly analogous to the laws of Boyle, Gay-Lussac and Avogadro concerning gases. The theory of the dissociation of electrolytes—salts, acids and bases—into their components, the ions (cations and anions), which we owe to Arrhenius, affords a satisfactory explanation of an enormous number of facts hitherto unintelligible. These newer doctrines not only correlate facts hitherto unconnected, but they have shown the way to new lines of experimentation and have acted as a most powerful stimulus to original research. While it is probably not true that chemical activity is due solely to ions and never to whole molecules, yet the number of chemical reactions which according to the physical chemists are purely ionic is very great, including certainly the majority thus far investigated. The studies of Kahlenberg and True on the toxic effects of acids and bases on plant life indicate that it is the hydrogen ion of the acid and the hydroxyl ion of the bases which is the active constituent. The significant experiments of Loeb on the power of muscle to absorb water in the presence of acids suggest the value of the physical-chemical method of thought in physiology. The work of Krönig and Paul upon the effects of disinfectant substances has made probable the ionic nature of this influence. The introduction by Dreser of the conception of the osmotic work done by the kidney and a calculation of the same in foot pounds is of the deepest interest, even if his interpretation of his results, as it would appear, has to be somewhat modified. The practical results in sight from the clinical studies by the method of physical chemistry undertaken by Hamburger, Köppe, Koranyi and others are being thankfully received by clinicians all over the world. Loeb of Chicago has recently interested us by proving the poisonous effects of pure solutions of common salt, and though his experiments have been upon lowly organisms, I should consider the medical man rash who continued to give a patient of low vitality large doses of ordinary salt solution when he can just as well introduce a solution in which the holding in a variety of salts corresponds more nearly to that of normal serum. Almost startling, too, is the assertion of Loeb that the eggs of echinoderms can be fertilized in the absence of spermatozoa by magnesium ions. If the phenomenon of fertilization—that *sanctum sanctorum* of physiological processes begins to be invaded by physical chemistry—what may we not expect from that science in the future. It would take too long to refer to other work in this field—to the constant reciprocal relation existing between chlorides and achlorides of the blood and urine, to the newer ideas on the occurrence of œdema, to the speculations concerning so-called ion-proteids. Suffice it to say, that the promise for the future in pathogenesis and in pharmacodynamics is much brightened by the advent of physical chemistry. Were a medical student, suited by heredity and environment to look forward to the higher things in medicine, to ask me the question, "How can I best fit myself to make real advances in knowledge in medicine and therapy during the next twenty-five years?" I should say, "In addition to a thorough medical course, arm yourself with sufficient mathematics and gain a thorough theoretical and practical training in the methods of physics and chemistry and especially in the principles and methods of what is called 'physical chemistry.' After this turn your attention to the solution of medical problems." Not that the doctrines of van't Hoff and Arrhenius will be able to clear up all difficulties—the doctrines themselves may even be found to be only helpful hypotheses and later be supplanted by others less faulty,* but all our knowledge is but relative, and at present new knowl-

* Some physicists are inclined to believe that the "corpuscular" doctrine advanced by J. J. Thomson seriously threatens the position of the ion-conception.

edge can probably be easiest reached by working with the methods referred to.

The conviction is not infrequently expressed that surgery having gone so far cannot have many great conquests still before it, but when we review recent progress it would seem hazardous to deny the possibility of still more interesting advances. The extensive use of local anæsthesia since the introduction of cocaine in 1884 has led to striking modifications in surgical technique. The general narcosis produced by ether and chloroform together with perfected hæmostatic methods had a tendency to encourage slow operations. With cocaine anæsthesia and infiltration of the tissues with nearly indifferent fluids surgeons have again been compelled to operate more quickly and with greater efforts at precision. The discovery of the X ray has made bone surgery much more accurate work than it could ever have been before. Most noteworthy, perhaps, in modern surgery, are the operations which are now undertaken upon the liver, gall-bladder and bile ducts. These together with gastrointestinal surgery have elevated abdominal surgery to even a higher rank than that attained by pelvic surgery through the activity of the gynæcologists. Progress can certainly be expected still in the treatment of surgical diseases. Max Broedel in Kelly's service has just shown us by a study of its blood-vessels the safest way to cut into the pelvis of the kidney.

The sharp line between medicine and surgery is breaking down. The two domains overlap at their boundaries and the importance of medical men and surgeons working together is becoming more and more appreciated. The establishment of a journal, the *Mittheilungen aus dem Grenzgebiete der Chirurgie und Medizin*, is an indication of the feeling which exists. The surgery of the future aside from emergency cases will be largely done in hospitals. Surgeons, to attain the necessary technical skill and familiarity with normal and pathological living tissues, must stand for years over an operating table. A trained corps of assistants and nurses is essential for the more difficult problems which now fall to the lot of the surgical specialist.

Compared with the brilliant achievements of the surgeon the therapeutic efforts of the physician are felt by most medical men as well as by the laity to be somewhat disappointing. In spite of the extraordinary keenness of diagnostic power which has been developed in internal medicine the painfully exact studies in pathological histology and in physiological and pathological chemistry, the wide-spread activity in pharmacological and pharmacodynamical experiment and the indefatigable efforts of the manufacturing chemist to supply new drugs, the view is prevalent and rightly so that in the treatment of internal diseases "we have more to hope for the future than to entrust to the present." The explanation is obvious. The age is one of doubt. Authority now less than ever before counts for anything. There is a lively fear of empiricism, an insatiable desire for rational explanation. Pathological anatomy stimulated to brilliant diagnosis, but, for a time at least, it encouraged therapeutic pessimism. Skoda, the type of a therapeutic nihilist even went so far as to say "we can diagnose disease, describe it and get a grasp of it, but we dare not expect by any means to cure it." In such a temper drugs of unknown physiological action cannot conscientiously be set to act upon bodily tissues in disease in which we are ignorant of the deviations from the normal of the chemical and physical processes going on in the cells. The death blow came first to polypharmacy; to-day, with many physicians, pharmacotherapy, as a whole, is almost moribund. Ask the prescription chemist how his work now compares with that of fifteen or twenty years ago. He will tell you that he is lucky if he fills ten recipes to-day, where he formerly filled a hundred. The druggist in the village or small town may still receive an occasional prescription which orders ten or fifteen varieties of herbs, but the fine old concoctions know to our fathers have almost entirely disappeared. It is seldom in this day that more than one or two drugs are prescribed at one time and these too often because "the patient must have something." A dozen drugs altogether suffice for the pharmacotherapeutic armamentarium of some of the most eminent physicians on this continent.

The reaction against the use of drugs, together with the development of the expectant method of treatment, permitted of a more accurate study of the natural cure of the disease than was before possible. Consistent homoeopathists who pushed their minimal dosage to such a degree that any conceivable drug effect was prevented did much, though unintentionally, to illustrate the healing power of nature unaided. Dietl's studies of pneumonia, treated without blood-letting, convinced him and the world that the effects of therapeutic interference in this disease had been greatly over-estimated.

Marked as have been the advantages derived from these therapeutic revolutions I cannot help but feel that the time has come for a more hopeful outlook for therapy in internal medicine. More thought among the best men might with advantage be given to it. Not that a whit less attention should be given to diagnosis or to pathological study—only through these is a successful therapy thinkable—but may we not interest ourselves more in the therapeutic measures of proven value which are really at our disposal. I am fully aware that some practitioners fail to properly diagnose their cases, that there are those who have but little scientific knowledge of disease, and it is these usually who possess the largest magazines of misplaced confidence in drugs. It may even be said to be certain that the majority of men in practice who leave it temporarily to undertake post-graduate work, would be benefited more by instruction in the wealth of diagnostic aids recently put at our disposal than by a course in therapeutics. That the skilled diagnostician, however, can be of greater service to his patients if he put the same keen, well-directed intelligence into motion with regard to treatment that he uses in diagnosis instead of stopping short at the diagnosis and shrugging his shoulders when therapeutic effort is mentioned, must be patent. As Leyden puts it: "The task of therapy is to help the patient as far as is possible with the

means at its disposal at the time; it dare not postpone the treatment to future discoveries. Specific therapy, long looked upon as that alone which is safe and worth striving for, is deprived of its absolute dominion; instead of 'curing diseases,' our task is altered to 'making patients well.'"

I cannot help but think that one of the causes of therapeutic pessimism among the better men in the profession lies in the fact that when therapeutics is spoken of most men call pharmacotherapy disproportionately into mind. It is because they are insufficiently known and appreciated that dietotherapy, climatotherapy, hydrotherapy, kinesiotherapy, electrotherapy and psychotherapy are not ranked with pharmacotherapy, and yet, in the majority of cases with which physicians deal, one or more of these is of far greater importance than treatment with drugs. Psychotherapy especially has a great future. Not until physicians become better psychologists and learn better how to apply psychic methods in the treatment of disease can we hope for the disappearance of such psychic epidemics as that represented by Christian science. In the near future psychopathogenic mechanisms should be carefully studied in order that psychoprophylaxis can have a wider field.

What the future of pharmacotherapy will be who will be rash enough to judge? That it will be great seems certain. That it cannot soon be great seems sure. Synthetic chemistry has supplied us with a host of new bodies for experimentation. Only a very small percentage of these have thus far been found to be of value. Antipyretics, analgesics and hypnotics especially are being multiplied. They have to be slowly tested on animals, then on healthy human beings and last of all on human beings in diseased conditions before their actual value can be ascertained. The effects of drugs like acetone-chloroform and urethane astonish us, however, and whet the appetite for further discovery.

No single system of therapy is likely soon again to hold general sway. *Contraria contrariis* and *similia similibus* have ceased among scientifically cultivated men to be a universal guide of therapeutic action. The biologically fundamental principle of Pflüger and Arndt, namely, that "minute stimuli, excite to vital activity, stimuli of medium strength favor it, strong stimuli inhibit it, strongest abolish it, it being, however, always an individual matter whether a given stimulus will prove to be feeble or one of medium strength or maximal," associated with the Ritter-Valli law that "diseased organs are in a state of heightened excitability" has been made by Oscar Schulz the basis of his "organ-therapy." Very valuable as the concept appears to be, medical men, with a caution born of experience, will be loath to accept it or any other generalization as an all-sufficient maxim.

The revival of organotherapy or opotherapy, as the French designate it, is a marked feature of present treatment. One of the oldest methods, having been employed long before the Christian era, opotherapy began with an attempt to produce an aphrodisiac effect by administering the genital organs of the respective sex to the individual who desired stimulation. It is rather curious that the present revival was inaugurated by Brown-Sequard, the composition of whose elixir vitae you know. Organotherapy has, however, this time a rational basis in the conception of an internal secretion, deduced by Brown-Sequard from the studies of Claude Bernard. The production of experimental cachexia thyreopriva and the bringing of the proof that the transplanted thyreoid would save an animal from the disease suggested the possibility of the use of thyreoid substance in myxœdema and cretinism with the marvellous results which most practitioners have by this time been permitted to observe. The chemical analyses of Baumann showed that an iodine compound in the normal thyreoid is an important element in the gland.

This "*Parenchymsaftherapie*," as Virchow designates it, is obviously a substitution-therapy—a restoration to the diseased body of chemical substances, the removal of which from the normal body gives rise to symptoms of disease. It is in atrophic conditions of the gland that the therapy is valuable. Myxœdema and cretinism are diseases which correspond to the "altruistic atrophy" of Hansemann, while Basedow's disease is thought by many to be an example of "altruistic hypertrophy." Had the principles underlying thyreoidtherapy been earlier recognized we should not have expected benefit from the administration of thyreoid extract in hypertrophic conditions of the gland.

The French are busy testing the effects of thyreoid-therapy on the healing of fractured bones. The experimentation is still in progress and it is too early yet to say much regarding it.

Ponfick's remarkable case, which makes it appear possible that the hypophysis and the thyreoid may be compensatory glands, will doubtless stimulate to further study.

With the advent of a successful thyreoid therapy, the notoriety hunters soon introduced organic extracts of the most various sorts. Cardin, cerebrin, hepatin were launched and vaunted. Examination of the manufacture of a certain prostate extract showed that it was being prepared from female animals! Such empirical attempts were worse than useless. They represent a return to the primitive.

With certain of the organs we are, however, provided with a rational basis for experimentation. Mering and Minkowski proved the disastrous effects upon the animal of extirpation of the pancreas. The diabetes which followed extirpation could be prevented by transplantation of pieces of pancreas. Yet for reasons not satisfactorily understood pancreas therapy has not been made practically useful.

Again, the effects of removal of the adrenals have been carefully studied. Addison's disease is believed to be largely the result of loss of adrenal substance. Unfortunately, the administration of adrenal extract, while it may alleviate some of the symptoms of Addison's disease, has no effect on the others. The attention paid to the adrenal of late by physiological chemists has, however, been most fruitful. The studies concerning the blood-pressure raising constituents are extremely valuable. The active substance has been isolated

and its chemical nature studied. The work of Abel and others upon epinephrin is furnishing most interesting data for future use.

Rhinologists are using adrenal extract as a vaso-constrictor in the nose. Fresh from the German press comes a careful paper by Stoelzner (in Heubner's clinic), detailing a large series of cases of rickets, markedly benefited by adrenal extract. He finds that the cranio-tabes, the sweats, the delayed coming of the teeth, the irritability of the vaso-motor system, the general restlessness and excitability, the curious smell of the urine, are all very markedly improved by the treatment. The softening of the thorax is frequently benefited. The spasm of the glottis and other symptoms of tetany, however, generally appear to remain uninfluenced by the adrenal extract. The improvement can frequently be made out during the first week of treatment. An amelioration of the symptoms goes on rapidly for a few weeks, later on more slowly.

The spleen and bone-marrow extracts which have been introduced increase the white and red corpuscles of the blood, possibly owing to the nuclein which they contain. That hypophysis extract is of no value in acromegaly would not be surprising, if acromegaly should turn out to be, as some investigators believe, rather an instance of "altruistic hypertrophy" in the sense of Hansemann than one of "altruistic atrophy."

One of the most recent advances claimed in opotherapy is the feeding of ovarian substance as a substitution-therapy in cases (1) where the ovaries have been removed at operation, and (2) at the climacteric to relieve the phenomena characteristic of that period. The substance is given in Germany in the form of Landau's oophorin tablets. Loewy and Richter report that this ovarian substance has a remarkable capacity for increasing the oxygenating power of the body-cells in cases in which the ovaries have been removed. Their protocols are very convincing. Whether or not the therapy will be useful in preventing the obesity so characteristic of so many such cases we must wait to see, but the Germans feel confident that it will.

The advances along the lines of opotherapy are sufficiently indicated by the foregoing experiences. Physiology, experimental pathology, physiological chemistry, pharmacology and pharmacodynamics must lead the way.

In the struggle against infectious diseases a rapid extension of the powers of the physician is observable. The resistance of human beings as a whole is being increased not only by the slow method of natural selection, but by a more rapid mode through personal hygiene. Prophylactic inoculations have been multiplied since the work of Pasteur. The cholera inoculation, that for pest and that for typhoid, appear to be valuable. Flexner in Philadelphia is now experimenting with a prophylactic against the bacillus dysenteriæ so deadly in its effects in the Philippine Islands and Japan. The introduction of Behring's serumtherapy in diphtheria has undoubtedly greatly reduced the mortality of that disease, indeed, diphtheria is now scarcely a disease to be dreaded. Aside from the serum against diphtheria, however, there is as yet little of practical value to acknowledge from this side.

The antidiphtheric serum is an antitoxic serum. That introduced against tetanus is also an antitoxic serum. To be ranked with these two is probably also Calmette's serum against snake poison. Tetanus serum is only preventive, not curative, possibly owing to the fact that the antitoxine injected subcutaneously or into the blood cannot reach the toxine when once the latter has combined with the protoplasm of the nerve cells. Even intracerebral introduction of the antitoxine is not fully satisfactory for obvious reasons. All the other sera which have been introduced, namely, those against cholera, the streptococcus, pneumococcus, the bacilli of plague, anthrax and typhoid fever are not antitoxic sera but antibacterial sera. They do not neutralize the poison which the bacteria produce but have the power of killing the bacteria in the body of the patient and of dissolving them up. Not a single one of these sera is as yet practically useful as a therapeutic measure.

Ehrlich's studies make it probable that with these antibacterial sera at least two bodies are necessary for successful action; (1) the *inter-body* or *immunizing body*, and (2) the *end-body* or *complement* (formerly called *addiment* by Ehrlich). The latter is present in normal serum and is the true dissolving body, but it can act only when it is bound to the bacterial cell by means of the immunizing body. The antibacterial sera are rich in the immunizing body. It may be possible that they are insufficient owing to there not being enough of the end-body present. Wassermann is now making experiments in this connection. He hopes that by increasing the amount of end-body or complement available that the antibacterial sera may be rendered valuable in the treatment of disease in human beings.

Had not this paper already become too long it would have been interesting to refer to the progress making in the treatment of conditions of autointoxication and of the so-called constitutional diseases, but I must forbear.

From what has been said it is obvious that we have no reason to be discouraged as regards the future of therapy, but rather cause for hope and enthusiasm. We have learned the secret of progress and some formulæ for daily action. The secret of advance lies in the consciousness of the fact that it is the orderly application of the well-trained intelligence to medical problems that alone yields valuable results—not the haphazard guess work of the ignorant and untrained mind. Prolonged technical education and systematic research lead to therapeutic advance. In daily life, in the application of discoveries already made, the quack and the routinist physician, with the healing power of Nature behind them, will cure many cases, but we can be sure that greater success and especially greater mental satisfaction will attend the efforts of the physician well educated in the various medical sciences who, thinking *all around and through his case*, arrives at the most accurate diagnosis possible and gives the patient the benefit of a well-planned conscientious treatment, utilizing every means

which will tend to his cure or relief. If this physician have a specific he will be glad to employ it; if radical cure be impossible he will not neglect the palliative; if at last the exitus lethalis cannot be prevented he will at least see that the end is euthanasic.

A COMPARATIVE STUDY OF SOME MEMBERS OF A PATHOGENIC GROUP OF BACILLI OF THE HOG CHOLERA OR BAC. ENTERITIDIS (GÄRTNER) TYPE, INTERMEDIATE BETWEEN THE TYPHOID AND COLON GROUPS.

WITH THE REPORT OF A CASE RESEMBLING TYPHOID FEVER, IN WHICH THERE OCCURRED A POST-FEBRILE OSTEOMYELITIS DUE TO SUCH AN INTERMEDIATE BACILLUS.

By Harvey Cushing, M. D.

(From the Laboratory for Surgical Pathology of The Johns Hopkins Hospital.)

The possibility that under varying conditions of environment different characteristics may be acquired by the members of the large typhoid-colon group of bacilli has inclined some investigators to regard them as closely related or even interchangeable organisms. Nevertheless, there are certain forms which possess, as ordinarily encountered, such definite cultural and pathogenic peculiarities, and which have a tendency to retain the same with such a degree of permanency, that they may be recognized as distinct and constant variations. That this applies to *B. typhosus* and *B. coli communis*, the extremes of the group, is too well known to be dwelt upon. There exists, however, intermediate to these forms, one especially recognizable subdivision, the clinical significance of which as a definite type has been much slighted.

The members of this particular intermediate group are bacilli which possess the morphological and motile properties of Eberth's bacillus but differ from this organism chiefly in the fermentation reactions, since they produce gas in the presence of glucose and other more easily fermentable carbohydrates. Their chief distinguishing feature from the bacillus of Escherich, on the other hand, rests upon the fact that fermentation in various media made from milk does not produce sufficient acidity to precipitate the casein, but, on the contrary, the acid production is but a transient process and is followed, in the presence of air, by a prompt (2-3 days) and distinguishing alkalinization of the media which furnishes a ready means of differentiation from both the typhoid and colon type.

Herbert E. Durham,[1] in 1898, boldly divided this whole family into three groups as follows:

I. The Eberth group including *B. typhosus* and its near allies.

II. The Gärtner group including *B. enteritidis* and its near allies.

III. The Escherich group including *B. coli communis* and its near allies.

He states in parentheses that the "allies" of the typhoid group are almost unknown,* while those of groups II and III have never been sufficiently worked out.

In this intermediate or Gärtner group Durham has placed the following organisms: *Bac. enteritidis* of Gärtner,[2] *B. Breslaviensis* (von Ermenghem),[3] *B. morbificans bovis* (Basenau),[4] the "Wurstvergiftung" bacillus described by Fischer,[5] *B. Friedebergensis* (Gaffky und Paak),[6] the Cotta "Fleischver-

[1] Durham, Herbert E.: On the serum diagnosis of typhoid fever, with especial reference to the Bacillus of Gärtner and its allies. The Lancet, Vol. I, p. 134, January 15, 1898.

* Organisms culturally indistinguishable from *B. typhosus* have been encountered in the surgical laboratory on several occasions during the past two years. These have been obtained from a perirenal abscess, from the urinary bladder and from peritoneal infections of intestinal origin unassociated with typhoid; on one occasion from the lumen of a chronically inflamed appendix. Similar organisms have been met with in the alimentary canal of healthy dogs. We have hesitated to regard these as *B. typhosus* from the absence of a definite reaction with typhoid serum though they are doubtless closely related forms. From what I have seen of Shiga's bacillus dysenteriæ, a specimen of which, obtained in the Philippines, was kindly given to me by Dr. Flexner, I should regard it also as an allied form of *B. typhosus*.

[2] Gärtner: Ueber die Fleischvergiftung in Frankenhausen am Kyffhäuser und den Erreger derselben. Correspondenz-Blätter des Allgemeinen ärztlichen Vereins von Thüringen. No. 9, 1888.

[3] Von Ermenghem: Recherches sur les empoisonnements produits par de la viande de veau à Morseele. Travaux du laboratoire d'Hygiène et de Bactériologie de l' Université de Gand. Tome I, fassicule 3, 1892.

[4] Basenau, Fritz: Ueber eine im Fleisch gefundene infectiöse Bacterie. (Bac. morbificans bovis.) Archiv für Hygiene. Bd. XX, S. 242, 1894, and XXXII, p. 219, 1898.

[5] Fischer, Bernhard: Ueber einige bemerkenswerthe Befunde bei der Untersuchung choleraverdächtiger Materials. Deutsche medicinische Wochenschrift, Jahrg. XIX, S. 575-598, 1893.

[6] Gaffky und Paak: Ein Beitrag zur Frage der sogenannnter Wurst-und Fleischvergiftungen. Arbeiten aus den kaiserlichen Gesundheitsamte. Band VI, S. 159, 1890. Also Deutsche med. Wochenschrift, Jahrg. XVIII, S. 297, 1892.

giftung" bacillus,[7] as well as the organisms described by Gunther,[8] Karlinsky,[9] Kaensche[10] and others.

These bacilli, it will be seen, come almost uniformly from meat-poisoning epidemics which occurred on the continent, and presumably they are the identical organism which Gärtner first described in 1888.*

Durham further believes that the gas-producing "typhoid" bacilli of various observers almost certainly belong to this group as well, and not improbably also those cases of "septicæmic typhoid fever" of French authors, in which death occurred before typical lesions had appeared and which were supposed to be due to Eberth's bacillus. In other words, there are possibly intermediate gas-producing forms of the typhoid-colon family which may be the cause of infections giving clinical symptoms easily mistaken for typhoid fever. This is of importance in relation to the cases which are to be described later.

Theobald Smith,[11] during his investigations concerning the bacteriology of infectious swine diseases in 1893, had noted the great similarity between *B. cholerae suis* and a variety of other pathogenic forms among which were Gärtner's *B. enteritidis*, Loeffler's *B. typhi murium*, a bacillus found in a mare after abortion, etc. He in consequence has since referred to them as members of the "Hog Cholera Group" of bacilli in much the same significance as Durham uses the term "Gärtner group." Unfortunately, however, owing to what seemed at the time (1885) an advisable change in terminology, the name hog cholera bacillus was given to an organism previously called swine plague bacillus and some misinterpretation has arisen abroad concerning the variety *B. cholerae suis* as it is now recognized in this country, from the confusion in nomenclature resultant to this change.*

Recent observations by Reed and Carroll[15] have further demonstrated that there is a close biological relationship between Sanarelli's *Bacillus icteroides* and *B. cholerae suis* and through their report has occasioned much discussion,[16] the former organism also doubtless belongs in the group under consideration. Some months previous to their published report, acting upon a suggestion of Dr. Welch, I had found that it was almost impossible to recognize any cultural differences between these organisms and bacilli of the *B. enteritidis* (Gärtner) type which I was studying.†

We thus see that the close biological relationship of many of these organisms has been recognized, though no attempt

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[7] Die Fleischvergiftung in Cotta. 21 Jahresbericht über das Medicinalwesen im Königreich Sachsen auf das Jahr, 1889, S. 104. Ref. Hygienische Rundschau, 1891, S. 716.

[8] Gunther, Carl: Bacteriologische Untersuchungen in einem Falle von Fleischvergiftung. Archiv für Hygiene, Bd. XXVIII, p. 146, 1897.

[9] Karlinsky, Justyn: Zur Kenntniss des Bacillus Enteritidis Gärtner. Centralblatt fur Bacteriologie, Bd. VI, S. 289, 1889.

[10] Kaensche. C.: Zur Kenntniss der Krankheitserreger bei Fleischvergiftungen. Zeitschrift für Hygiene, Bd. XXII, S. 53, 1896.

* This was found under the following circumstances:

In Saxony a diseased cow had been slaughtered and the flesh sold for food. Fifty-seven people who had eaten of this meat became ill, the severity of symptoms being directly proportionate to the amount consumed and inversely to the thoroughness of cooking. One young working man ate 800 grams raw, and died in about 35 hours. Gärtner isolated from the flesh of the diseased cow and the organs of this fatal case his so-called *B. enteritidis*. Durham himself[12] has encountered the same organism in the liver of a fatal case from an epidemic in England, and he alone among English writers has concerned himself with these infections. In his valuable address[13] given at Oldham in 1898 he lays especial stress upon the importance of *B. enteritidis* as the cause of the various meat-poisoning epidemics and describes his observations on the Chatterton outbreak.[14]

[11] Smith, Theobald, and V. A. Moore: Additional investigations concerning infectious swine diseases. Bureau of Animal Industry, U. S. Department of Agriculture. Bulletin No. 6, p. 10, 1894.

[12] Durham, Herbert E.: An epidemic of gastro-enteritis associated with the presence of a variety of the bacillus enteritidis (Gärtner). British Medical Journal, Vol. II, p. 600, Sept. 3, 1898.

[13] Durham, Herbert E.: An address on the present knowledge of outbreaks due to meat poisoning. British Medical Journal, Vol. II, p. 1797, Dec. 17, 1898.

[14] Bowes and Ashton: An outbreak of Food Poisoning; being a report on 35 cases of veal-pie poisoning occurring in Chatterton. British Medical Journal, Vol. II, p. 1456, Nov. 5, 1898.

* Kruse in 1896 (C. Flügge, Die Microorganismen, Zweiter Theil, S. 401) describes the present *B. chol. suis* of American writers under the name *Bacillus suipestifer*, which he places in the Hemorrhagic Septicæmia group.

[15] Reed, Walter, and James Carroll: Bacillus Icteroides and Bacillus Choleræ Suis—a preliminary note. The Medical News, Vol. LXXIV, p. 513, April 29, 1899.

[16] 1. Sanarelli, G.: Some Observations and Controversial Remarks on the Specific Cause of Yellow Fever. The Medical News, Vol. LXXV, p. 193. Aug. 12, 1899.

2. Sternberg, Geo. M.: The Bacillus Icteroides as the Cause of Yellow Fever. A Reply to Professor Sanarelli. Ibid. Aug. 19, 1899.

3. Reed and Carroll: The Specific Cause of Yellow Fever. A Reply to Dr. G. Sanarelli. Ibid. Sept. 9, 1899.

4. Novy, F. G.: The Bacillus Icteroides. A Reply to Dr. Sanarelli. Ibid. Sept. 23, 1899.

5. Sanarelli, G.: The Bacteriology of Yellow Fever once More. Ibid. Dec. 9, 1899.

† The culture of *B. icteroides* which was used had been originally obtained from Roux's laboratory and was but one removed from Sanarelli's original organism. Dr. Reed has since kindly furnished me with three varieties of *B. icteroides* obtained from Santiago and Havana. These organisms belong to the Gärtner group and possess no cultural characteristics sufficient to distinguish them from *B. enteritidis* or *B. choleræ suis*. Differences in pathogenic activity in man and animals and in the serum reactions doubtless exist just as do variations in pathogenicity among members of the *B. coli* group, and consequently to state that the hog cholera bacillus is culturally indistinguishable from *B. icteroides* does not seem to me necessarily to indicate that the latter may not be the cause of a specific infection (yellow fever). As will be seen in the experiments on pathogenic action, the serum test alone is a means of distinguishing members of the group and cultural similarities are by no means an indication of equalities in pathogenic virulence.

has been made to classify them on other grounds than variations of pathogenicity in which peculiarity the individual members of a species naturally differ within wide limits, which in no way affects phylogenetic relationship. The variability in nomenclature itself shows how little recognition has been paid to the similarity of cultural as well as of clinical and pathologic manifestations of the members of this intermediate group.

In 1897 Widal [17] described an organism which was isolated from an œsophageal abscess some years after an attack of typhoid fever, and adopting the nomenclature of Gilbert [18] he designated it a "paracolon" bacillus. With this organism he grouped several others having similar characteristics, as the bacillus psittacosis of Nocard and the "microbe de la septicémie des veaux" of Thomassen.[19] From Widal's brief description it would seem that this organism is a member of the intermediate group under discussion. It was an actively motile bacillus producing no indol and fermenting glucose but not lactose. Widal's claim for specificity of this particular type was based on the definite serum reaction which the patient's blood showed toward the organism.

The terms paracolon and paratyphoid, however, Durham does not consider at all appropriate, as the members of the group are quite distinct from both *B. typhosus* and *B. coli*.

Gwyn [20] in 1898 reported a remarkable case which occurred in Dr. Osler's clinic and which presented all of the clinical symptoms of typhoid fever, but in which no serum reaction was at any time demonstrable toward the *Bacillus typhosus*. From the blood of this patient Gwyn isolated in pure culture an organism having cultural characteristics akin to the Gärtner group, and which under the influence of Widal's terminology he designated as a "paracolon." Toward this organism the patient's serum had an agglutinative reaction in further evidence of the infection. The failure on repeated examinations to demonstrate any serum reaction toward *B. typhosus* was of course not conclusive evidence of the absence of typhoid fever, but the query was naturally raised whether the clinical symptoms could not have been due entirely to an infection with the isolated "paracolon" alone. Of the several hundred cases of typhoid fever which have occurred in Dr. Osler's service since the employment of the Widal-Gruber reaction has become a routine measure of confirming diagnosis, only a few individual cases have failed to show a definite agglutinative reaction toward *B. typhosus*. It is not impossible that these cases may have represented infections with members of the intermediate group. Durham mentions in his paper a personal experience with an infection resembling a mild typhoid, after which he found a persisting serum reaction toward *B. enteritidis* and which he naturally accredited to a presumable original infection with this bacillus.

A case recently entered the surgical wards (Dr. Halsted's) of The Johns Hopkins Hospital which furnishes the subject of this communication. An organism almost identical with that of Gwyn's and belonging to or closely allied to the Hog Cholera or Gärtner group was isolated from an abscess of the rib which appeared during the convalescence from a prolonged fever of enteric type. That a general infection had occurred was clear from the specific action of the patient's serum toward the isolated organism; there was no agglutinative reaction whatever evidenced toward *B. typhosus*. Whether this infection was of intestinal origin and occurred through the atrium afforded by typhoidal lesions or whether it was in itself the cause of the fever, must remain undecided, though it seems from these two cases not impossible that a prolonged fever with the clinical picture of typhoid may be induced by the members of this intermediate group. Had there been a mixed infection, one would have expected a double agglutinative reaction which was not present.

CLINICAL SUMMARY.

Typhoid fever (?) with relapse. Costochondral osteomyelitis during convalescence. Abscess with rupture six months later. Persisting sinus for three months, showing pure culture of intermediate bacillus at operation.

Case. Surgical No. 8753. M. Burley, colored, aged 27, was admitted into Dr. Halsted's service, March 1st, 1899, with the following history: From early in June, 1898, nine months before admission, he had suffered with a prolonged course of fever extending over a period of ten weeks. A note from his physician, Dr. Hammond, of Jessups, Maryland, describes the case as one of typhoid with a severe but typical clinical course. The history is without particular note except that he had a distinct relapse of the fever which was ushered in by a profuse hemorrhage from the nose. During his convalescence, the patient says that he had noticed two tender nodules near his breast bone, one the size of a dollar, the other somewhat smaller. The latter subsequently disappeared but the larger one increased in size and six months later broke open, evacuating a large amount of pus. Since that time it has continued to discharge, the sinus persisting without tendency to heal permanently, though it has closed on several occasions for a short period.

Examination showed the opening of a sinus, lined by pale granulations and discharging a small amount of pus, situated on a level with the fifth rib at the edge of the sternum. There were slight œdema of the surrounding tissues and tenderness for a few centimetres along the course of the fifth rib. A probe could be inserted for five centimetres downward and to the left about to the junction of the rib and cartilage where a grating bony substance could be felt.

The patient's physical examination was otherwise negative.

[17] F. Widal: Séroréaction dans une infection à paracolibacille. La Semaine Médicale, 4 août, 1897.

[18] Gilbert: De la Colibacillose. Semaine Médicale. 1895, p. 1-3.

[19] Thomassen, M.: Une nouvelle septicémie des veaux. Annales de l'Institut Pasteur. Tome XI, p. 523, 1897.

[20] Gwyn, Norman B.: On Infection with a Paracolon bacillus in a case with all the clinical features of typhoid fever. The Johns Hopkins Hospital Bulletin, Vol. IX, p. 54. March, 1898.

No clumping reaction could be demonstrated toward *B. typhosus* with the patient's serum.

Operation March 6th, 1899. The sinus and surrounding tissues, with a button of chest wall including the cartilage of the adjoining ribs were excised and the wound closed over a blood clot by a plastic skin flap.

The tissues removed consisted of the cartilage and portion of bone of the diseased rib. A cavity measuring about one cm. in diameter lined with pale granulation tissue was situated in the cartilage near the end of the bone. A sinus led from this through the cartilage toward the sternum. No bone formation could be demonstrated in this cartilage. The cartilages of the adjoining ribs (6th and 7th), portions of which were excised as described, showed marked evidence of beginning ossification as a fine network of new bone-formation preventing easy section with the knife.*

Cultures were taken at the operating table from the bottom of the sinus immediately on making the first incision into it. These cultures showed a pure growth of a bacillus which fermented glucose and did not coagulate milk. Appreciating the rarity in such situations of bacillary forms other than *B. typhosus*, the organism was carefully examined with the results to be appended, namely, its identification as a member of the intermediate, the Hog Cholera or Gärtner group. For convenience this bacillus will hereafter be called *Bacillus O*.

Agglutination reactions with the isolated organism.

The following early observations upon the agglutinative reactions of the patient's serum toward the isolated organism and toward other members of the typhoid-colon family which were at hand, as well as a comparison with the reactions of sera obtained from other sources toward these same organisms were kindly made for me by Dr. Gwyn. Unfortunately, at this time the relation of *B. chol. suis* and *B. icteroides* with the organism in question was not recognized, and not until later did I come into possession, through the courtesy of Dr. Durham, of Gärtner's bacillus, *B. morbificans bovis* (Basenau) and the variety "Hatton" which Durham has described. When these organisms were received, three months after the operation, I found that the patient's serum had so far lost its reaction toward the intermediate bacilli that the results were unsatisfactory for comparative purposes and none of the original serum had been saved. This, however, was compensated for by comparing results with the serum obtained from an immunized animal, as will be described later.

(A) Effect of a variety of sera upon *Bacillus O*, the organism isolated from the abscess.

I. Reactions with patients' serum. Two observations with 10-hour cultures showing active motility. A marked immediate reaction * occurs in slight dilutions, with instant cessation of motion and the formation of large clumps, in ½ to 2 minutes. Reaction is slower but distinctly marked in a 1–800 dilution in two hours.

II. Reactions with other agglutinating sera. Typhoid sera, A., B. and C., agglutinating *B. typhosus* in dilutions of 1–400. All were quite negative in dilutions of 1–10 in two hours. The motility in all cases was but slightly if at all affected.

III. Reactions with sera of healthy individuals. Five normal sera were tried in dilution of 1–10. The reaction was absolutely negative in all cases.

(B) Effect of the patient's serum upon other agglutinable organisms of the typhoid-colon group.

I. *Bacillus typhosus* reacting well to typhoid serum in dilutions of 1–200 and 1–300. Little or no effect upon motility in two hours in dilution of 1–10.

II. *B. coli communis*. Six varieties from stock cultures of the pathological laboratory.

A.	Motility active.	Dilution 1–200	Well marked clumping. Motility not absolutely stopped in two hours.
B.	Motility slight.	Dilution 1–50	Fair reaction in two hours.
C.	" very sluggish	" 1–10	Fair reaction in one hour.
D.	" " "	" 1–10	No appreciable effect in one hour.
E.	" " "	" 1–10	
F.	" " "	" 1–10	

III. *B. Paracolon* (Gwyn). Motility very active. Dilution 1–10. Slight evidence of reaction. Cessation of motility.

*It is noteworthy that postenteric and traumatic osteomyelitides in children almost invariably have their starting point in the epiphyseal ends of the long bones of the extremities, while only in adults do we find similar processes originating at the costochrondral articulations. The natural explanation seems to be that the seat of most active bone-formation is especially susceptible to infectious processes. In adults the cartilages of the ribs represent practically the only situation where ossification in cartilage is taking place. The occasional seat of post-typhoidal infection in the thyroid cartilage of adults may be accounted for in similar fashion. In a post-typhoidal case operated upon two years ago at this hospital by Dr. Finney, I had an excellent opportunity of examining the tissues, since there had been no preformed sinus and the infected area with portions of the two neighboring ribs had been removed *in toto*. The abscess had apparently started in the cartilage of the sixth rib close to the rib itself, where ossification, as was seen by comparing sections of the cartilages of the adjoining ribs, had been in progress. A pure culture of *B. typhosus* in this case was obtained from the cavity in the cartilage.

*For a reaction to be *positive* we understand that there must be a complete cessation of motility, with clearing of the field of individual organisms and the formation of large clumps. The figures may seem low, but "a reaction" is looked upon very critically.

(C) Comparison of the effect of the typhoid and normal sera used in (A), II and (A), III upon these same organisms of (B).

	Typhoid serum	Normal serum (a)	Normal serum (b)
B. typh.	1–300 Positive.	1–10 Negative.	1–10 Negative.
B. coli A.	1–100 Positive.	1–10 Positive.	1–10 Positive.
B. coli B.	1–50 Suggestive.	1–10 Suggestive.	1–10 Suggestive.
B. coli C.	1–10 Negative.	1–10 Suggestive.	1–10 Negative.
B. coli D.	1–10 Suggestive.	1–10 Positive.	1–10 Positive.
Paracolon (Gwyn)	1–10 Negative.	1–10 Negative.	1–10 Negative.

These results show the absence of any reaction on the part of the patient's serum toward *B. typhosus* or toward any other organism tried except an occasional variety of *B. coli*. It is, however, a not uncommon observation to find an agglutinative reaction toward colon, since sera from apparently healthy individuals, as the above results demonstrate, often react in some degree toward members of the colon group, doubtless from the more or less frequent slight colon infections which occur in the course of occasional mild enteritides. In the absence, therefore, of a double agglutinative reaction we may with propriety exclude the possibility that the infection with *Bac. O* was superimposed upon a typhoidal infection and that the former organism and not *B. typhosus* was responsible for the clinical symptoms.

Note on the Pathology and Bacteriology of the Lesion.

The isolation of this organism from an osteomyelitic process secondary to an enteritis and the positive agglutinatve reaction of the patient's serum toward it are conclusive evidence of a peripheral septicæmia, such as frequently occurs during the progress of enteritides occasioned by *B. typhosus*. It is, of course, possible that many of these intermediate organisms may have their habitat at one time or another in the intestine and, through the atrium afforded by lesions such as occur in typhoidal enteritides, they may enter the portal circulation, or, indeed, by way of the thoracic duct, the peripheral circulation, provided they are not checked by the mesenteric glands. Thus a peripheral septicæmia, such as in typhoid fever frequently occurs from an invasion with the specific organism of the disease itself, may supposedly be occasioned by the entry of any intestinal bacterium. Such a secondary invasion Dr. Welch,[21] in 1890, demonstrated to be possible with *B. coli*, but it has been a common observation that in such superimposed colon infections the organisms only exceptionally pass beyond the confines of the abdominal cavity.* It is therefore exceedingly unusual to find in peripheral post-typhoidal lesions organisms of *intestinal* origin other than the typhoid bacillus itself, though complicating pyogenic skin (coccal) organisms are common. The abdominal complications, occurring in the liver and gall-bladder, for example, by way of the portal circulation are, on the other hand, frequently due to such secondary invasion. For these reasons, as well as those given above, it seems unlikely that *Bac. O* was such a secondary invader. In suppurative sequelæ, in bone especially, it has been exceptional, if we may draw conclusions from such lesions as have occurred secondary to typhoidal enteritides, to find intestinal bacilli other than the specific organism of the disease. As has been stated, the latter is frequently present in the peripheral circulation and, as Quinke[23] has demonstrated, it finds the bone-marrow a habitat of especial predilection. Of the fifty-one cases of post-typhoidal bone lesions which Keen[24] collected, and in which authentic bacteriological studies had been made, thirty-eight were associated with a pure or mixed infection with *B. typhosus*. In only one case was there a supposed mixed infection with *B. coli*, which naturally would be the most common secondary invader. This was a case of Klemm's.[25] Déhu[26] (1893) in his elaborate statistics stated that *B. coli* had never been seen in bone abscesses and without excluding the possibility of its occurrence he regarded it as extremely improbable that the colon bacillus held any relation to the production of ostitides.

Recently Blumer[27] has reported a case in which *B. coli* was supposed to have been isolated from a post-typhoidal rib abscess. His organism, however, was an alkali-producer in milk and therefore probably did not ferment lactose and should hardly be regarded as a colon bacillus. No mention occurs of serum reactions in his report, and it is quite possible that the organism isolated was the specific cause of the fever preceding the osteomyelitis and was a member of the group in question.

Bacteriological Survey of the Bacillus. (*Bac. O.*)

For purposes of comparison inoculations were made upon all media, with the following organisms:*

[21] Welch, Wm. H.: The Bacillus Coli Communis; the Conditions of its Invasion of the Human Body, and its Pathogenic Properties. Medical News, Vol. LIX, p. 669, Dec. 12, 1891.

* This has been discussed in a recent paper.[22]

[22] Observations upon the Origin of Gall-Bladder Infections and upon the Experimental Formation of Gall Stones. The Johns Hopkins Bulletin, Vol. X, Nos. 101-102, p. 166, 1899.

[23] Quinke, H., und A. Stühlen: Zur Pathologie des Abdominal typhus. Typhusbacillen im Knochenmark. Berliner klinische Wochenschrift, Bd. XXXI, No. 15, p. 351. April 9, 1894.

[24] Keen, W. W.: Complications and Sequels of Typhoid Fever. Philadelphia, 1898, p. 113.

[25] Klemm: Quoted by Keen, op. cit., p. 113.

[26] Déhu, Paul: Etude sur le rôle du bacille d'Eberth dans les complications de la fièvre typhoide. Thèse de Paris, 1893, p. 91.

[27] Blumer, George: A Case of Post-typhoid Bone Inflammation due to the Colon Bacillus. The Pacific Record of Medicine and Surgery, Vol. XIII, p. 105, November 15, 1898.

* 1-2-3-4-5-9-10-11 were obtained through the kindness of Dr. Harris from the laboratory stock cultures. To Dr. Harris and his assistants, Mr. Winnie and Mr. Holden, I am indebted for confirmation in some of these observations. 6-7-8 were obtained from Cambridge through the courtesy of Dr. Herbert E. Durham. Three additional varieties of *B. icteroides* from different sources were kindly sent to me by Dr. Reed from Washington.

1. *B. typhosus* (a), an early alkali-producer (3 weeks);
2. *B. typhosus* (b), a late alkali-producer (months);
3. *B. coli communis* (a), var. not fermenting saccharose;
4. *B. coli communis* (b), var. fermenting saccharose;
5. *B. paracolon* (Gwyn);
6. *B. enteritidis* (Gärtner);
7. *B. morbificans bovis* (Basenau);
8. *B. var.* "*Hatton*" of Durham;
9. *B. choleræ suis;*
10. *B. icteroides* (Sanarelli);
11. *B. typhi murium* (Loeffler);

thus giving a variety of intermediate forms, as well as the chief variations in the extreme groups of colon and typhoid.

MORPHOLOGY, ETC.—*Bacillus O* could not be distinguished from the typhoid bacillus in form or staining qualities and its description is therefore unnecessary. It decolorized by Gram. Variations in size were observable upon different media and occasionally sedimenting organisms were found to take a bipolar stain. Flagella in number and distribution resembled those of *B. typhosus*. Twelve to fourteen were counted on some specimens and occasionally exceedingly long terminal flagella were observed. Of the above bacilli it is possible that Basenau's organism (No. 7) alone could have been distinguished from the rest with any degree of probability. The variety which Dr. Durham had presented tended to grow in filamentous forms quite recognizable upon most media.

Active motility was present with all varieties except those of *B. coli* which, under the same cultural conditions, showed very sluggish movements, or no motility whatever. The motility of *Bac. O* was especially active, being darting in character, and remained present for many days.

AGAR AND GELATIN.—The appearance of colonies and of the surface growth upon these media presented no features by which they could with any certainty be distinguished. All were very typhoid-like, the luxuriance of surface growth depending somewhat upon the initial reaction. Basenau's organism again is perhaps an exception, as the surface colonies on gelatin presented a more irregular fringed edge than the others which ordinarily showed a pale brownish-yellow centre fading toward the periphery; this was usually slightly scalloped, well defined and almost colorless.

GROWTH IN BOUILLON.—*Bacillus O* and Gwyn's "paracolon" in bouillon and similar media grew much less luxuriantly than did the various intermediate forms used for comparison. The hog cholera and Gärtner type cloud the media very rapidly and more abundantly than *B. coli*, and usually a surface pellicle is formed which may or may not fall. The former organisms, on the contrary, produce but slight turbidity and thus resemble the typhoid rather than the colon end of the group. One series of bouillon inoculations, the medium having an initial reaction of + 1.2 (that is, 1.2 cc. of a normal tenth standard solution of sodium hydroxide was required to neutralize 10 cc. of the medium), gave after five days of incubation the following reactions:*

B. coli (a).

Branch. Slightly cloudy; large bubble of gas. Initial reaction + 1.2; terminal reaction + 1.6; production of acidity .4 per cent.

Bulb. Very cloudy; abundant precipitate; slight pellicle. Initial reaction + 1.2; terminal reaction + 1.6; production of acidity .4 per cent.

B. typhosus.

Branch. Very slight cloud; no gas. Initial reaction + 1.2; terminal reaction + 1.4; production of acidity .2 per cent.

Bulb. Slight cloud; slight precipitate. Initial reaction + 1.2; terminal reaction + 1.4; production of acidity .2 per cent.

Bacillus O.

Branch. Very slight cloud; small bubble of gas. Initial reaction + 1.2; terminal reaction + 1.3; production of acidity .1 per cent.

Bulb. Slight cloud; abundant precipitate; no pellicle. Initial reaction + 1.2; terminal reaction + 1.0; production of alkalinity .3 per cent.

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Branch. Very slight cloud; small bubble of gas. Initial reaction + 1.2; terminal reaction + 1.4; production of acidity .2 per cent.

Bulb. Very cloudy with abundant precipitate and pellicle. Initial reaction + 1.2; terminal reaction + 0.9; production of alkalinity .5 per cent.

It is thus seen by the cloudiness of the closed arm and by the acid produced that a carbohydrate present in ordinary bouillon permits all of these organisms to grow anaërobically. The intermediate (Gärtner) and colon forms with their allies produce a small amount of gas. The aërobic growth in the open bulb remains acid in the case of colon and typhoid but produces with the rapidly growing Gärtner type some degree of alkalinity, which in a short time is sufficient to overcome the preliminary acidity.

GROWTH IN DUNHAM'S SOLUTION AND DEXTROSE-FREE-BOUILLON WITH INDOL REACTIONS.—In *dextrose-free-bouillon* the vigor of growth of the Gärtner-Hog Cholera type is especially well shown, the great cloudiness and rapid formation of surface pellicle, most marked with *B. typhi murium* and *B. morbif. bovis*, being very characteristic. *Bac. O* and Gwyn's organism here again grow much more like the typhoid

* The percentage of reactions given throughout this paper represents the amount of normal sodium hydroxide or oxalic acid solution requisite to neutralize, by the phenolphthalein test, 10 cc. of the fluid in question. For the purpose of titration normal tenth solutions were used. In all cases an uninoculated control, having undergone corresponding incubation and exposure, was similarly tested to give the initial reaction. As recommended by the committee of American bacteriologists,[2] the plus and minus signs are used to indicate respectively acidity and alkalinity.

[2] Procedures Recommended for the Study of Bacteria: Submitted to the American Public Health Association in Phila., Pa., Sept., 1897. Rumford Press, Concord, N. H., 1898.

bacillus. The same may be said of their growth in *Dunham's solution.*

In the latter medium after seven days incubation no indol could be demonstrated for any of the intermediate forms, while *B. coli* gave its usual marked reaction. Theobald Smith, however, has shown[29] that the carbohydrate which Dunham's peptone solution (generally used for this test) contains, exercises a restraining action on the production of indol, while in dextrose-free-bouillon * there is no such retardation. A careful test, therefore, was made for *B. typhosus*, *B. coli com.*, *Bac. O* and *B. paracolon* (Gwyn) on the principles laid down by Dr. Smith, and by this means very slight traces of indol, not apparent in Dunham's solution, were appreciable for the two latter organisms after the 8th, 9th and 10th days. The method employed was as follows:

Daily, over a period of ten days, four tubes of dextrose-free-bouillon (properly tested for muscle sugar) were inoculated respectively with a typhoid, colon, paracolon (Gwyn) and Bacillus O and placed in the thermostat. At the end of this period all 40 tubes were tested at the same time for indol with freshly prepared standard solutions. The colon bacillus showed after 24 hours a faint trace of indol which increased in intensity up to the 10th day. With typhoid no trace was demonstrable. Gwyn's paracolon on the 8th, 9th and 10th days showed a faint trace and similarly *Bacillus O* in the older tubes gave evidence of a slight production of indol, possibly a little more than the paracolon. These reactions were positive, though slight, and might readily have been overlooked on a single tube test. In Gwyn's original report a belief is expressed in the non-production of indol. On another occasion a similar series of inoculations for comparison with the other members of the intermediate group gave no reaction whatever for any of the organisms up to the 10th day. The culture of *Bac. O* used at this time was several generations removed from the original.

Apparently, from Peckham's elaborate observations,[30] the reaction for indol should not be given the prominence in questions of differentiation of bacillary types that has been attributed to it by Kitasato and other writers who have regarded this as a most important and distinguishing characteristic of *B. coli communis.* According to the source of the culture, however, and possibly depending upon the proteid characteristics of the nourishing medium, there is great variability in indol production, which, if the observations of de Klecki, Dreyfuss, Sanarelli and others are to be depended upon, is in some degree a measure of pathogenicity. Peckham has shown that *in vitro* this property of indol production may be made to vary within wide limits by cultivation on various media. Indeed she has been able to obtain an indol producing typhoid and to cause *B. coli* to lose this property. As ordinarily encountered in the human body, however, *B. coli* produces indol, and the members of the intermediate group under discussion barely appreciable amounts, if any, through the forms *Bac. O* and Gwyn's paracolon were obtained from sources and under conditions which, according to Peckham, would have been most favorable, if the colon observations are a standard, toward the acquisition of this characteristic.

Growth on Potato.—This is a very uncertain means of differentiation. *B. coli* doubtless grows more luxuriantly on this medium and shows more marked chromogenetic properties. All depends, however, upon the initial reaction of the potato. Occasionally the intermediate bacilli have been seen to grow almost like *B. typhosus*, at other times almost as profusely as colon, but on such occasions the typhoid bacillus itself after a longer incubation would present the same appearance. *Bac. O* and *B. paracolon* (Gwyn) behaved like typhoid, *i. e.*, grew more slowly, darkened the potato less rapidly and assumed a yellow color later than the other intermediate varieties. On one occasion a series of inoculations was made on potato which had an initial reaction of + 8.0.* All of the intermediate forms of Gärtner type gave an abundant, visible, slightly elevated, smooth, glistening, opaque growth of light-yellow color in 24 hours, which deepened in 48 hours, with an accompanying discoloration of the potato. In four days the potato had assumed a dirty-gray color for all these intermediate forms. *B. typhosus*, *Bac. O* and *B. paracolon* growing more slowly finally gave the same appearance in six days or more. At the end of four days in the presence of the Gärtner type the potato had a reaction of — 4.0, thus 12 per cent of alkalinity had been produced by the growth of the organism in this time. The unreliability of the potato reaction is thus exemplified. These intermediate forms, as well as *B. typhosus*, are alkali-producers when grown in the presence of air, and this alone is responsible for the change in appearance of the medium. This may be demonstrated by adding a corresponding amount of alkali to the potato and incubating it for a few hours, when it assumes the same dirty-gray color. *B. coli*, however, produces its abundant growth without formation of alkaline products, the medium remaining free from the discoloration of the alkali-producers.

[29] Smith, Theobald: A Modification of the Method for Determining the Production of Indol by Bacteria. The Journal of Experimental Medicine, Vol. II, p. 543, 1897.

* For method of preparation cf. Smith, Theobald, Ueber Fehlerquellen bei Prüfung der Gas-und Säure-bildung bei Bakterien und deren Vermeidung. Centralblatt für Bakteriologie, u. s. w. Band XXII, 1897, No. 2/3, S. 49.

[30] Peckham, Adelaide Ward: The Influence of Environment upon the Biological Processes of the Various Members of the Colon Group of Bacilli. The Journal of Experimental Medicine, Vol. II, p. 549, 1897.

* These reactions were roughly made by titrating 5 cc. of a neutral solution, in which the potato had been shaken up for five minutes, both before inoculation and 5 days after the growth. Presumably this represents but a small measure of the true reaction.

MILK.—The reactions in milk and the various media made from it, depending upon the variations in the rapidity and degree of acidulation or alkalinization of the medium, constitute one of the most important means of differentiation of members of the typhoid-colon family.

B. coli, as is well known, acting upon its carbohydrate constituents, acidulates milk up to the point of precipitation of the casein (6-8 per cent of acidity) in periods varying from two to seven days and at the same time there is a liberation of gas amounting to about 1/6th of the closed arm of a fermentation tube. Here acidulation ceases, the organism dying out or being inhibited in its growth by the acid formed. That the organism is capable of producing a larger amount of acid from the contained carbohydrates is shown by the coagulation of milk which, having acquired a previous alkalinity of 4 per cent from the growth of an intermediate form, is subsequently inoculated with *B. coli*, which not only overgrows the original organism but overcomes its alkali-production and finally precipitates the casein which this had held in solution.

B. typhosus also is an acid-producer but, unlike colon, not to the degree of coagulation of the medium. If plain milk requires 6 per cent to completely precipitate the casein, milk in which *B. typh.* has been grown for 48 hours requires but 4-5 per cent. There are varieties, however, which when grown in milk in the presence of air, lose their acid reaction and become neutral or alkaline. Occasionally this is a noticeable and early change, occurring in a few weeks, and has given rise to the name "blue typhoid" from the unusual color which follows its growth in litmus milk. It is a characteristic, however, which seems to belong remotely to all examples of *B. typhosus*.

The intermediate bacilli under discussion have a very different action in milk, namely, that of an early and distinctive alkalinization of the medium in the presence of air, which appears after a transient acidity of a few hours. This alkalinization progresses up to the point of solution of the casein (about 4 per cent of alkalinity) and thus with the liberation of the fat-globules gives to the medium the peculiar greenish opalescence and translucency which has been said to be characteristic alone (?) of the Hog-Cholera bacillus, but which occurs similarly from the growth of all members of the group and in fact without the bacteria can be occasioned by the addition of a coresponding amount of alkali to the milk. This reaction in the presence of the growing organisms begins to be apparent in about two weeks, that is, sufficient alkali has been produced to partly dissolve the casein and render the milk slightly translucent. After entire solution has taken place (4-6 weeks) the liberated fat-globules, freed of their enclosing casein envelopes, are found floating upon the surface, leaving the medium fairly clear, often with a gelatinous clot at the bottom of the tube, consisting chiefly of a mass of organisms which take a feeble and bipolar stain and are apparently dead. The opalescent medium above contains a comparatively small number of viable evenly staining bacilli.

The accompanying photographs (Plate VIII, Fig. I (a) and (b)) of a series of tubes show the appearance of this reaction in the case of the intermediate bacilli contrasted with that of *B. typhosus*, *B. coli* and a control tube, all of which have retained their original opacity. Boiling has no apparent effect on the milk which has undergone this change.

In litmus milk the transient acid reaction * and subsequent alkalinization are shown by the color changes. The opalizing reaction from solution of the casein, if present, is not apparent in the litmus medium. The bulb of the fermentation tube after a few days acquires a blue color which deepens in time to a dark navy blue corresponding to the color which follows the addition of 4 per cent or more of alkalinity to a control tube. At varying periods, during the activity of growth, at the bottom of the test-tube or in the closed arm of the fermentation tube the litmus becomes reduced and colorless. These reactions all take place more slowly with *Bac. O* and Gwyn's paracolon, and in fact Gwyn did not recognize this terminal alkalinity of milk, which does not occur for 12 to 14 days. The neutralization period for *Bac. O* does not appear till the 8th day. This relative slowness in alkalinization should hardly separate these two varieties from the Gärtner or Hog Cholera type any more than that slow production of acidity sufficient to precipitate casein should separate one variety of colon from another which coagulates milk in half the time.

These results may be expressed as follows:

1. Colon acidulates milk up to the point of precipitation of the casein in from 2 to 7 days.

B. coli. **Seven-day growth in fermentation tube of milk having an initial reaction of + 2.2. Total gas ⅓. Coagulation of milk in 2 days.**

Reaction { **Branch (terminal) + 8.8 less 2.2 = 6.60% acid produced.**
Bulb (terminal) + 8.8 less 2.2 = 6.60% acid produced.

2. Typhoid produces in milk from 1–2 per cent of acidity, not enough to coagulate the medium. In other words, it requires 1–2 per cent less of acidity to precipitate the casein after the growth of *B. typhosus* than in control milk. Further, as Theobald Smith [1] has shown, the addition to milk in sufficient amounts of a carbohydrate, such as dextrose, which can be acted upon by *B. typhosus*, will lead to the coagulation of the medium.

*** This slight early acidification in milk, so rapidly overcome by the production of an alkaline product, is presumably due to the presence in milk of traces of a fermentable substance which Theobald Smith believes to be a second carbohydrate, possibly dextrose. Neither *B. typhosus* nor any member of the intermediate group appears to have any reducing effect upon lactose in otherwise sugar-free media. For this reason the reactions in lactose sugar-free bouillon and in milk are not supplementary as ordinarily supposed.**

[1] Theobald Smith: The action of typhoid bacilli on milk, and its probable relation to a second carbohydrate in that fluid. The Journal of the Boston Society of Medical Sciences, Vol. II, No. 12, p. 236, June, 1898.

B. typhosus. **Seven-day growth in fermentation tube of milk having initial reaction of + 2.2. No gas. No coagulation.**

Reaction { Branch (terminal) + 3.8 less 2.2 = 1.60% acid produced.
Bulb (terminal) + 3.8 less 2.2 = 1.60% acid produced.

3. *The intermediate type* produces a transient acidity followed by a marked alkalinity in the presence of air which increases from 0 per cent in 3 days to 4 per cent in two weeks with solution of the casein and the consequent production of partial translucence of the medium. This, however, only occurs in the presence of air. Such opalization does not occur in the closed arm of the fermentation tube. When such a reaction has occurred the addition of 4 per cent of acidity will again render the medium opaque and 10 per cent (6 per cent of acidity must be reached) must be added to precipitate the casein formerly held in solution by the alkali. Thus there is 10 per cent difference of reaction between the point of coagulation produced by the acid of *B coli* and the point of solution of the casein produced by the alkali of the intermediate group.

B. Gärtner et al. **Seven-day fermentation reactions with milk of + 2.2 initial reaction. Total gas = bubble. No coagulation.**

Reaction { Branch (terminal) + 3.8 less 2.2 =1.60% acid produced (cf. B. typhosus (2)).
Bulb (terminal) + 0.2 less 2.2 + 1.6 = 3.60% alkali produced.

3a. The allied forms, *Bac. O* and *B. paracolon* (Gwyn) show a corresponding but slower reaction.

Bac. O, **etc. Fermentation reaction in plain milk (7 days) with initial acidity of + 2.2. Gas bubble +. No coagulation.**

Reaction { Branch (terminal) + 3.9 less 2.2 = 1.70% acid produced (cf. B. Gärtner (3)).
Bulb (terminal) + 0.6 less 2.2 + 1.7 = 3.30% alkali produced (cf. 30% less than with Gärtner type in same time).

Fermentation Reactions with Various Sugars.

A valuable means of distinguishing varieties of the colon-typhoid group lies in their reactions in the presence of various carbohydrates. Theobald Smith regards this process of differentiation as most essential; "a relief from the uncertainty of the usual potato culture and the variable intensity of the indol reaction." The methods which he advocates were adopted and his precautions observed. Several series of inoculations were made with most of the organisms in the list which has been given, in fermentation tubes of sugar-free bouillon containing 1 per cent of glucose, lactose, mannite or saccharose sugars. The rapidity of gas-production was daily registered at the level of fluid in the closed arm; the proportion of CO_2 to explosive gas was finally noted and the reactions of the bulb and closed arm at varying periods were made an object of record and comparison. All of the observations were made during incubation at a temperature of 37° C. The original bouillon * in all instances, to insure its freedom from muscle sugar, was tested by inoculation and incubation with a gas-producing organism before its sugar percentages were added.

Reactions in Lactose. Owing to the observations of Smith, which have been reviewed above, upon the presence in milk of a fermentable substance other than lactose, some reservations must be made to the common belief in the correlation between the reactions in plain or litmus milk or in the litmus whey of Petruschky,[22] on the one hand, and the reactions occurring in media made by adding the carbohydrate to an otherwise sugar-free bouillon. In consequence of this fact a source of error may creep into the observations upon the fermentation of lactose, since the commercial product made from milk may be adulterated with this second carbohydrate. Similarly, mistakes may arise owing to the ease with which during the sterilization of lactose media some of the carbohydrate may be converted into a simple and more readily fermentable sugar. For this reason preparation in the autoclave should be avoided and the fractional method of sterilization be employed for this as well as for saccharose media. Furthermore, failure to insure complete freedom from muscle sugar in the original bouillon may lead to mistaken observations and it is doubtless due to these possibilities of error that so many conflicting statements are encountered regarding the fermentation of lactose by various bacteria. The accompanying photographs (Plate IX, Figs. 2 and 3), representing series of inoculations into lactose media, show how such erroneous observations may originate. In the series reproduced in Fig. 2 gas production was present in slight amount in all instances except with *B. typhosus*, and was presumably due to some dextrose adulteration. In the latter series, shown in Fig. 3, the original bouillon had not been completely freed from muscle-sugar, fermentation of which gave a small amount of gas. Before the addition of the 1 per cent lactose to the medium used in this series a corresponding amount of gas was produced in it by the inoculation with *B. coli communis*. Fig. 4 represents the typical reaction, *B. coli* alone producing gas from the carbohydrate, the other organisms producing no fermentative change whatever.

In the following table are given the reactions occurring in bulb and branch of the fermentation tube resultant to the growth of these organisms in 1 per cent lactose media. The figures throughout these tables represent the amount of normal tenth sodium hydroxide or oxalic acid solution required to neutralize by the phenolphthalein test 10 cc. of the medium. An uninoculated control was in each instance similarly tested and these results represent the calculated production of alkali or acid. It will be seen that the figures for the intermediate group are practically the same in all cases.

* For methods of preparation cf. Theobald Smith, p. 546.

[22] Petruschky, Johannes: Bakterio-chemische Untersuchungen. Centralbl. f. Bakteriologie. Bd. VII, S. 1, 49, 1890.

COMPUTED REACTION* AFTER 8 DAYS' INCUBATION WITH 1% LACTOSE SUGAR-FREE BOUILLON HAVING INITIAL ACIDITY OF 1.40%.

	B. typhosus (a).	Bacillus O.	B. paracolon (Gwyn).	B. morbif. bovis.	B. var. "Hatton."	B. enteritidis.	B. chol. suis.	B. icteroides.	B. typhi mur.	B. coli comm. (a).	B. coli comm. (b).
Reaction of Bulb	Alkaline .40%	Alkaline .95%	Alkaline .90%	Alkaline 1.60%	Alkaline 1.00	Alkaline 1.00%	Alkaline .80%	Alkaline 1.60%	Alkaline 1.60%	Acid 3.60%	Acid 4.2%
Reaction of Branch	No change	No change	No change	Alkaline .20%	Alkaline .10%	Alkaline .10%	Alkaline .10%	Alkaline .20%	Alkaline .20%	Acid 3.60%	Acid 3.6%
Total Gas.....	0	0	0	0	0	0	0	0	0	1/2+	3/4
Proportion of H/CO_2 ..	%	%	%	%	%	%	%	%	%	2+/1	2+/1

* The reactions represent the amount of acidity or alkalinity produced, and are computed from the initial reaction.

B. coli ferments lactose, producing an equal amount of acidity in closed arm and bulb, and gas composed of CO_2 and an explosive element (hydrogen) in the proportion of 1:2. No acid is produced by *B. typhosus* from pure lactose, despite the fact that ordinary milk is acidulated by its growth. The amount of alkalinity in the bulb, which occurs with this organism as well as with *Bac. O* is slightly less than that which follows the growth of the intermediate bacilli, possibly owing to the fact that they grow with less luxuriance than the intermediate variety, which, in the presence of air, multiply rapidly in bouillon. Theobald Smith states that alkali production bears a distinct relation to vigor of growth. The slight alkalinity of from .1 to .2 per cent in the closed arm with the more rapidly growing intermediate forms may be due to some interchange of reaction with the very alkaline medium in the bulb.

COMPUTED REACTIONS IN DEXTROSE SUGAR-FREE BOUILLON HAVING INITIAL ACIDITY OF 1.50%.

	B. typhosus.	Bacillus O.	B. paracolon (Gwyn).	B. morbif. bovis.	B. var. "Hatton."	B. enteritidis.	B. chol. suis.	B. icteroides.	B. typhi mur.	B. coli comm. (a).	B. coli comm. (b).
Reaction of Bulb	Acid 3.50%	Acid 3.50%	Acid 3.60%	Acid 3.70%	Acid 3.70%	Acid 3.70%	Acid 3.70%	Acid 3.70%	Acid 3.70%	Acid 3.90% 4.10%	Acid 3.80% 4.10%
Reaction of Branch	Acid 3.50%	Acid 3.70%	Acid 3.70%	Acid 3.90%	Acid 3.90%	Acid 4.10%	Acid 3.90%	Acid 4.15%	Acid 4.15%	Acid 4.15% 4.50%	Acid 3.90% 4.50%
Total Gas.....	0	1/3—1/2	1/3—1/2	2/3—1/2	2/3—1/2	2/3—2/3	2/3—1/2	1/3—2/3	2/3—1/2	1/2+	1/2—
Proportion of H/CO_2...	%	2+/1	2/1	2+/1	2+/1	2+/1	2+/1	2+/1	3/1	2/1	2/1

Reactions with Dextrose. All of the members of the Hog Cholera or Gärtner group produced gas, in correspondence with *B. coli* and its allies, when grown in the presence of dextrose. The total displacement in the closed arm of the fermentation tube was found to vary somewhat under different conditions of inoculation. Two series as represented in the photographs (Plate X, Figs. 5 and 6) are given in illustration of this irregularity. One feature, however, is brought out in each series, namely, the relative slowness of gas-production with the two allied forms, *Bacillus O* and Gwyn's *paracolon*, which in the first twenty-four hours produce less than half as much gas as the other organisms.

Reactions with Mannite. Like dextrose, this carbohydrate is readily fermented by the organisms in question (cf. Plate XI) with the production of even a greater amount of gas, which, under some circumstances (cf. Fig. 8), may displace the larger part of the fluid in the closed arm. In this series *Bac. O* was, as in the presence of dextrose, slow in its liberation of gas. One peculiarity of the reactions with mannite lies in the terminal reaction of the bulb which remains neutral or slightly alkaline, as does the media containing non-fermentable sugars (lactose and saccharose). The proportion of CO_2 in the gas was less than with dextrose, being 1/3 or less of the total amount. In several instances there was failure to demonstrate that the remainder contained any H or other explosive element.

Reactions with Saccharose. In the preparation of saccharose bouillon, as well as with lactose, precautions must be taken during sterilization to avoid any conversion of the carbohydrate into more readily fermentable sugars. No gas is produced and no acid formed by any of the intermediate group in this medium. Certain forms of *B. coli* also fail to

ferment saccharose, as is shown in Plate XII, Fig. 9. This has been pointed out by Theobald Smith. Other varieties of colon produce an abundance of gas, as is shown in Fig. 10 (*B. coli comm.* (b)). In the series presented in this latter photograph there had been a slight conversion of the sugar as the medium had been autoclaved. In several instances, consequently, a slight production of gas has resulted, showing the source of error which may result from this method of sterilization. The slowness of the growth of *Bacillus O* and Gwyn's *paracolon* heretofore commented on was shown in the closed branches of these tubes by the tardy reduction and decolorization of the litmus which had been added to the media. This is apparent in the photograph. In the accompanying table are given the reactions which occur after growth in saccharose media. It will be seen that the more rapidly growing organisms have produced a greater percentage of alkalinity in the presence of air and that a small percentage (.2 per cent) is present in the closed arm, possibly due as in the case of lactose reactions to some interchange in reaction with the bulb. The initial reaction of the medium in this series was + 1.0 and the reaction for the Gärtner or Hog-Cholera type after 9 days when the tests were made was + .8 for the closed arm and — 1.4 for the bulb. On the occasions when there was slight gas-production due to faulty preparation of the medium, a sufficient amount of acidity was found to delay alkalinization in the bulb.

TABLE OF COMPUTED REACTIONS IN 1% SACCHAROSE SUGAR-FREE BOUILLON.

	B. typhosus.	Bacillus O.	B. paracolon (Gwyn).	B. morbif. bovis.	B. var. "Hatton."	B. enteritidis.	B. cholerae suis.	B. icteroides.	B. typhi mur.	B. coli comm. (a).	B. coli comm. (b).
Reaction of Bulb	Alkaline 2.0%	Alkaline 2.0%	Alkaline 2.0%	Alkaline 2.4%	Alkaline 2.4%	Alkaline 2.4%	Alkaline 2.4%	Alkaline 2.4%	Alkaline 2.4%	Alkaline 2.4%	Acid 5.0%
Reaction of Branch....	Neutral.	Neutral.	Neutral.	Alkaline 0.2%	Alkaline 0.2%	Alkaline 0.2%	Alkaline 0.2%	Alkaline 0.2%	Alkaline 0.2%	Alkaline 0.2%	Acid 5.0%
Total Gas..... (cf. Plate V).	0	0	0	0	0	0	0	0	0	Occasional bubble.	⅝
Proportion of H/CO_2 ..	%	%	%	%	%	%	%	%	%	?	2+/1

Pellicle formed on bulb with 4, 5, 6, 7, 8, 9. Reactions taken on 9th day. Five days of original incubation.

Scraped-Tube Reaction.

For the differentiation of closely related bacilli, Achard and Renault[33] originated a method of inoculation of one organism upon a base which previously had served for the growth of another allied form. The development of the growth upon such a substratum was regarded as evidence of individuality and its failure as evidence of identity of the organisms. Many inoculations of this nature were made in the following way: After 72 hours of incubation at 37° C., the growth from the upper half of an inoculated agar slant was carefully removed and the tubes replaced in the thermostat to insure no further growth. Inoculations of these tubes were then made in a single streak along the centre of the area formerly occupied by the original growth and the results recorded after 72 hours of further incubation. How much reliance is to be placed upon this method of Achard is undetermined. Smith[34] does not regard it as an important criterion, since slightly increased sensitiveness to acids or alkalies which may characterize closely related organisms may affect it.

It can be seen on consulting the table that none of the organisms could furnish a visible growth when reinoculated on their original substratum. In the case of *Bacillus O*, both typhoid and colon grew on its original surface of growth, while none of the allied forms grew with any luxuriance. Gwyn's *paracolon* did not furnish any growth, but on the contrary *Bac. O* grew well upon the substratum of the *paracolon*. Similarly, although *B. coli* grew well upon the base of *Bac. O*, the latter gave no growth whatever on a colon substratum, though this was repeated with eight varieties of colon. It can, however, be said that the members of the intermediate group under most circumstances in which the reactions were tried failed to show on a substratum of one of its allies a growth of any vigor.

Thermal Death-Point.

Tests made by Mr. Winnie to determine the thermal death-point showed that an exposure at 60° C. for five minutes would prevent further growth of *Bacillus O*. A corresponding incubation at 55° C. failed to completely destroy the organisms, many colonies appearing on plate culture. Similarly, after a ten-minute exposure at the same temperature,

[33] Achard et Renault: Sur les bacilles de l'infection urinaire. Semaine Médicale, 1892, p. 136. Sur les différents types de bacilles urinaires appartenant au groupe du bacterium coli. Ibid., 1892, p. 512.

[34] Smith, Theobald: Notes on the Bacillus Coli Communis and Related Forms. American Journal of Medical Sciences. Vol. CX, p. 283, 1895.

a number of colonies appeared, though many less than after the shorter period of incubation.

PATHOGENICITY.

The object of this study has been merely an attempt at classification, and a lack of correspondence in pathogenic action may be no indication of the absence of phylogenetic relationship. Nevertheless, the following experiments, undertaken with some of these bacillary forms under discussion, are not without their instructive features. Most of the organisms which are members of this intermediate group possess pathogenic properties of considerable virulence toward animals and may be the occasion of epidemics in hogs, cattle and other live stock, mice, birds, etc., and toward man as well as animals, as is evidenced by the various epidemics of meat-poisoning, yellow fever, etc.

Pathogenic experiments have never been undertaken with Gwyn's *paracolon*, and the notes concerning *Bacillus O*, found under somewhat similar circumstances in a case clinically one of typhoid fever, show that its virulence toward the lower animals in the condition of its isolation was not an intense one, but resembled the action of *B. typhosus* rather than that of other members of the Gärtner or hog-cholera group.

SUBSTRATUM OF— / TRANSPLANT OF—	Bacillus O.	B. coli.	B. paracolon.	B. typhosus.	B. enteritidis.	B. var. "Hatton."	B. choleræ suis.	B. icteroides.	B. morbif. bovis.	B. typhi. mur.
Bacillus O	No growth	Good growth	No growth	Good Growth	No growth	Faint	Faint	No growth	Faint	Faint
B. coli	No growth	No growth	Faint	Faint	No growth	....	....	....	....	....
B. paracolon	Good growth	Fair growth	No growth	Faint	No growth	....	....	....	....	....
B. typhosus	No growth	Good growth	Fair growth	No growth	Fair growth	....	....	....	....	....
B. enteritidis	No growth	....	No growth	....	No growth	....	....	....	No growth	....
B. var. "Hatton"	No growth	...	....	....	....	No growth	....	....	No growth	....
B. chol. suis	Faint	....	....	....	....	....	No growth	....	....	....
B. icteroides	No growth	....	....	....	....	....	....	No growth	....	....
B. morbif. bovis	No growth	....	....	....	....	....	....	....	No growth	....
B. typhi mur	No growth	....	....	....	....	....	....	....	....	No growth

A mouse was killed in 24 hours by a large subcutaneous inoculation of an 18-hour bouillon culture. The autopsy revealed lesions typical of an acute general septicæmia. A guinea-pig inoculated subcutaneously with a number of organisms sufficient in amount to invariably be fatal in the case of *B. chol. suis*, recovered after a small local area of induration which persisted for a week or two. Rabbits inoculated intravenously with large doses recovered after an acute illness and an occasional local lesion. No intraperitoneal inoculations were made.

Possibly the most interesting feature of the animal experiments lies in the fact that although the serum of an animal which had recovered from an inoculation did not possess any very marked agglutinative properties toward the other bacilli related to that which had been inoculated; nevertheless, a certain protective immunity seemed to have been acquired. For example, a rabbit which had recovered from several infections with *Bac. O* and whose serum agglutinated this organism in 1–5000 dilution, recovered after an intravenous inoculation with a large dose of *B. chol. suis*, which was fatal to a control rabbit in a few hours. When killed 25 days later the former animal was found to have typical hog-cholera lesions in the liver and elsewhere. Animals killed by infections with *B. enteritidis* had similar lesions in the liver, gall-bladder, duodenum, etc., and in fact the liver necroses do not seem to be characteristic of any one of these varieties, but merely to represent focal destructions of liver substance by accumulations of organisms present in too great abundance for elimination. There can likewise be seen in all cases lesions of the gall-bladder, with clumped organisms in the bile, which shows the usual changes seen in enteric diseases, of the gall-ducts and of the duodenum which is usually deeply injected and from which the organisms of infection may usually be isolated.

One observation of especial interest was the occurrence in the liver of a rabbit which had rapidly succumbed to an overwhelming dose of *B. choleræ suis*, of extensive fatty degeneration of the liver-cells resembling very closely the condition which is seen in the liver of human beings who have died from yellow fever. It is unusual to find this change in the livers of animals experimentally inoculated with *B. icteroides*, and this has been used as an argument against the possibility that Sanarelli's bacillus could be the cause of yellow fever and its characteristic hepatic degeneration.

Results of Experimental Inoculations.

White Rabbit I. Weight 1600 gms. Serum does not react to any member of the intermediate group.

July 13th, 1899. Inoculation in posterior ear vein with one cc. of a 24-hour bouillon culture of *Bac. O.*

July 15th. Ear greatly swollen. Animal quite ill. Refuses food. Temp. 106°.

July 16th. Temperature 104°. Much better.

July 17th. Apparently well. Lively. Eating.

July 20th. Blood taken for serum reaction. Thrombus in ear vein at seat of inoculation. Cultures from thrombus show subsequently several colonies of *Bac. O.* Serum agglutinates *Bac. O* in 1–700 dilution. Reaction complete in 30 mins. No reaction in dilution of 1–50 with *B. enteritidis, B. morbificans bovis* or *B. "Hatton."*

July 22nd. Reinoculated in other posterior ear vein with two cc. of 24-hour culture of *Bac. O.* Animal remained quite ill for several days. Recovered.

July 28th. Apparently well. Blood-culture negative. Serum reaction positive in 1–4800 dilution. Comparative serum reactions with other bacilli: *B. chol. suis* 1–200, fair reaction. *B. enteritidis* (Gärtner et al.) 1–10, negative.

The slight agglutinative reaction toward *B. chol. suis* suggested that the animal had acquired some resistance against hog cholera and a large fatal dose was given to this animal and to a control animal with the following results:

White Rabbit I.

August 8, 1899. Intravenous inoc. of 1 cc. of 24 hour bouillon culture of *B. chol. suis.*

Aug. 10. Rabbit well.

Aug. 20. Blood taken for serum reactions shows a reaction toward *Bac. O* and *B. chol. suis* in 1–5000 dilution.

Control animal, of same weight with negative serum reactions.

Aug. 8. Corresponding inoculation.

Aug. 9. Found dead (18 hours.)

Autopsy. General septicæmia. No mac. changes except injection of duodenal mucosa and an acute cholecystitis with bile thin and pale. Stained preparations from all organs, urine and bile showed a multitude of bacilli.

Cultures. Heart-blood, liver, gall-bladder, peritoneal cavity, and kidneys, *B. chol. suis* pure; urine, *B. chol. suis* and *B. Coli communis.*

Organs. Acute fatty degeneration of the liver.

August 28th. Comparative serum reactions of White Rabbit I * with uninoculated organisms of the intermediate group as well as with *B. typhosus* showed that a slight tendency to agglutination more marked than before the last inoculation had been acquired. The reactions were as follows:

Organism.	Dilution.	Reaction.
Bacillus O.	up to 1–5000	Positive.
Bac. chol. suis.	" " 1–5000	"
B. icteroides	" " 1–100	"
B. typhosus	" " 1–200	"
B. enteritidis (Gärt.)	" " 1–50	"
B. var. " Hatton "	" " 1–10	"
B. morb. bovis	" " 1–10	Negative.
B. typh. mur.	" " 1–10	"
B. paracolon (Gwyn)	" " 1–10	"
B. coli com.	" " 1–10	"

1. Orig. culture from Roux's laboratory. Serum reaction positive up to 1–200, suggestive to 1–1000 in 2 hours.

2. B. icteroides from Santiago case, 1898. Serum reaction positive to 1–50; suggestive to 1–200 in 2 hours.

3. B. icteroides from Havana case, 1899. Serum reaction positive to 1–200; suggestive to 1–1000 in 2 hours.

Believing from these results that the animal had acquired in some degree a protective reaction toward other members of the intermediate group, although the clumping reaction was not marked in high dilutions, it was then inoculated with a fatal dose of *B. enteritidis* (Gärtner), as was also a normal control animal and another rabbit which had been immunized to *B. typhosus.*

Inoculation with Bac. enteritidis (Gärtner).

White Rabbit I. Serum reactions given above (Aug. 28).

Aug. 30. Inoc. in post. ear vein with 1 cc. of a 24-hour bouillon culture of *B. enteritidis* (Gärtner).

Aug. 31. Ill.

Sept. 1. Animal killed. Immediate autopsy. Caseous tubercle of ear at site of original *Bac. O* inoculation. (July 13.)

Abdomen. All organs apparently normal except liver and biliary apparatus. Section of former showed small focal necroses. Gall-bladder normal in appearance but containing bile which was thin and pale and which had a yellow precipitate showing through the thin bladder walls. This consisted of desquamated cells and amorphous precip. of bile pigments. No organisms identified. Duodenal mucosa showed several minute hemorrhages in upper 5 cm. Duodenal papilla was erect and injected.

Cultures. Tubercle of ear, heart-blood, kidney and liver, sterile. *From the gall-bladder an "intermediate" bacillus was isolated which could not be identified culturally. Identified by serum reaction, however, and shown to be Bac. enteritidis (Gärtner), as serum taken from rabbit with pure Gärtner infection clumped the organism in 1-500 dilution and had little effect on hog cholera and Bac. O.*

Duodenum. An unidentified intermediate bacillus was isolated, presumably *B. Gärtner,* in pure culture.

Sections of the liver showed areas of focal necrosis involving whole lobules.

Black Rabbit—normal control.

Serum reactions negative in 1–10 dilutions to *Bac. O, B. chol. suis, B. enteritidis* and *B. typh.*

Aug. 30. Corresponding inoculation. (Cf. White Rabbit I, Aug. 30.)

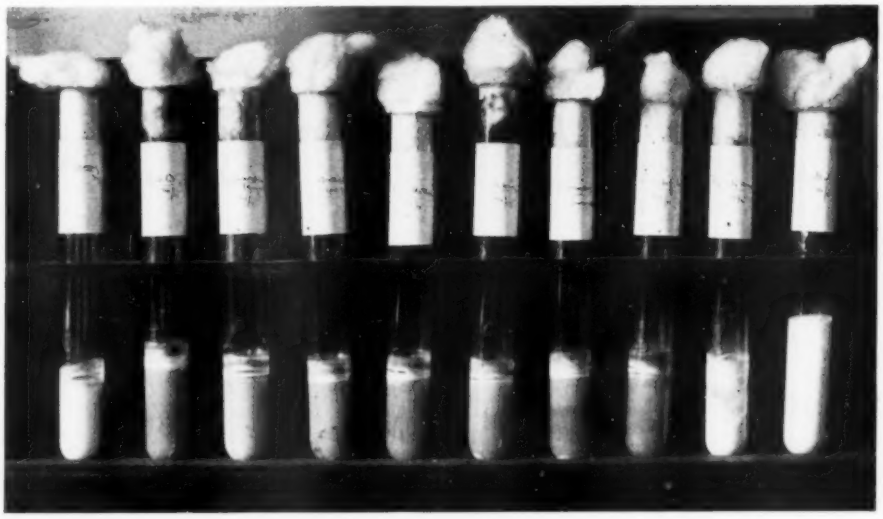
Aug. 31. Very ill.

Sept. 1. Found dead.

Autopsy. No decomposition.

Abdomen. Stomach full of food. Urinary bladder distended. No macroscopical changes apparent except in the bifiary apparatus and duodenum. The gall-bladder was distended and injected; full of hemorrhagic bile containing a flocculent precipitate.

* Agglutinations were also positive with this serum, having a high reaction toward *B. chol. suis,* toward three individual cultures of *B. icteroides* (Sanarelli), sent by Dr. Reed from the Washington laboratory as follows:



1. B. typh. 3. B. paracolon (Gwyn). 5. B. var. "Hatton." 7. B. icteroides. 9. B. coli.
2. Bac. O. 4. B. enterit. (Gärt.) 6. B. chol. suis. 8. B. morb. bov. (Bas.) 10. Control.

FIG. 1 (a)—Photograph of reactions in plain milk after 4 weeks. The diminution in opacity of the intermediate forms is well shown. Paracolon (Gwyn), producing alkali more slowly than the others, has not yet reached 4.0 per cent necessary for complete solution of the casein. B. chol. suis and B. icteroides have been shaken up and show the temporary settling of the surface layer of liberated fat-globules.

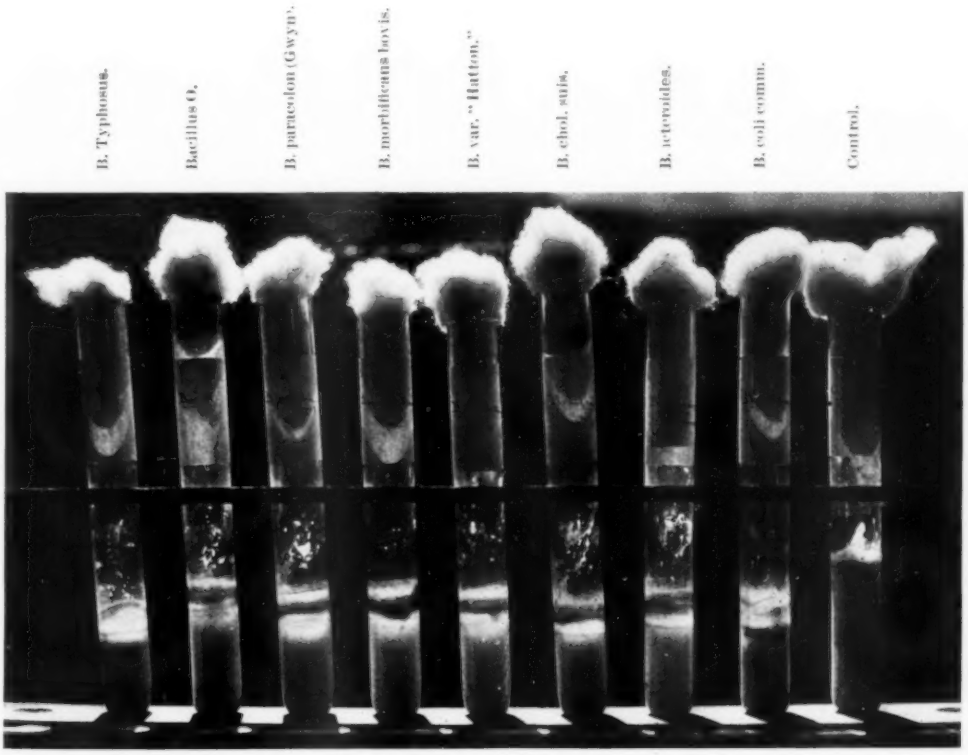
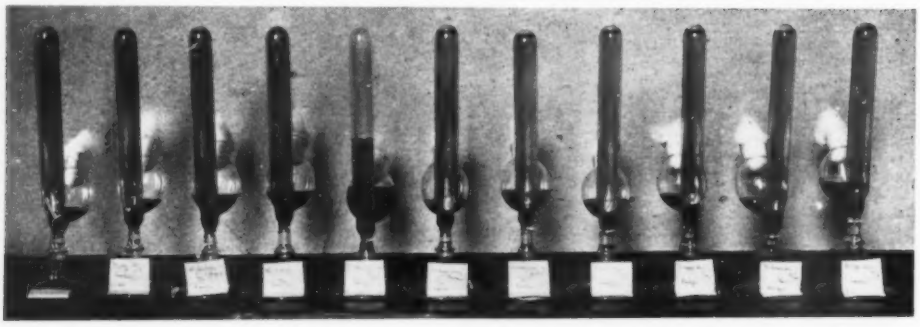
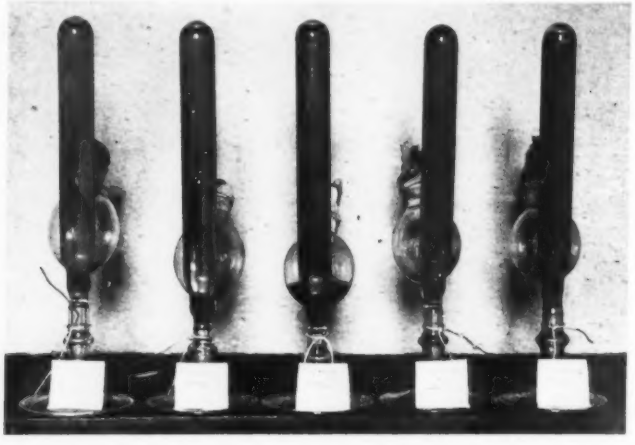


FIG. 1 (b)—Photograph taken with transmitted light of the same tubes as Fig. 1 (a), showing the comparative translucency of the intermediate group.



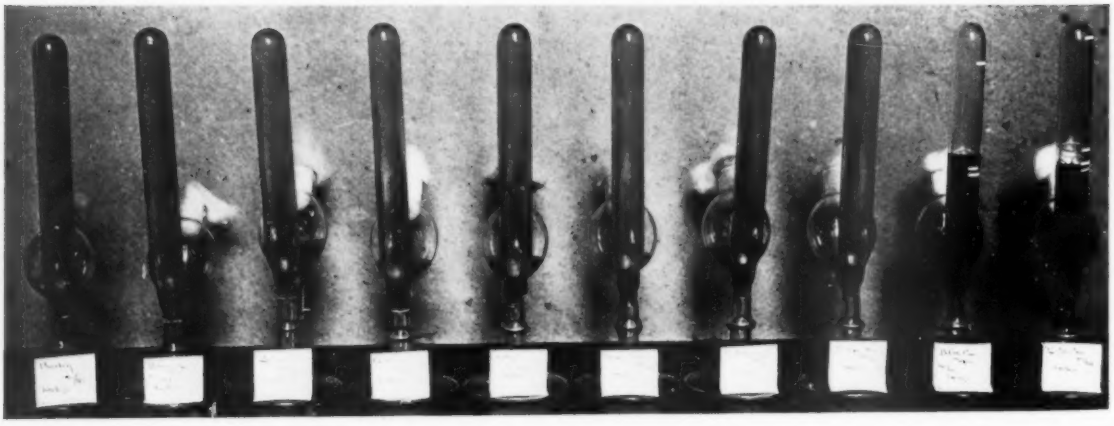
Control. B. paracolon. B. coli comm. B. ent. (Gärt.) B. chol. suis. B. typhi mur.
Bac. O. B. typhosus. B. morb. bovis. B. var. "Hatton." B. icteroides.

FIG. 2.—Reactions in sugar-free bouillon containing 1 per cent of commercial lactose. Gas-production slight in intermediate group due to dextrose (?) adulteration.



B. morbif. bovis. B. chol. suis. B. icteroides.
B. enteritides. B. paracolon.

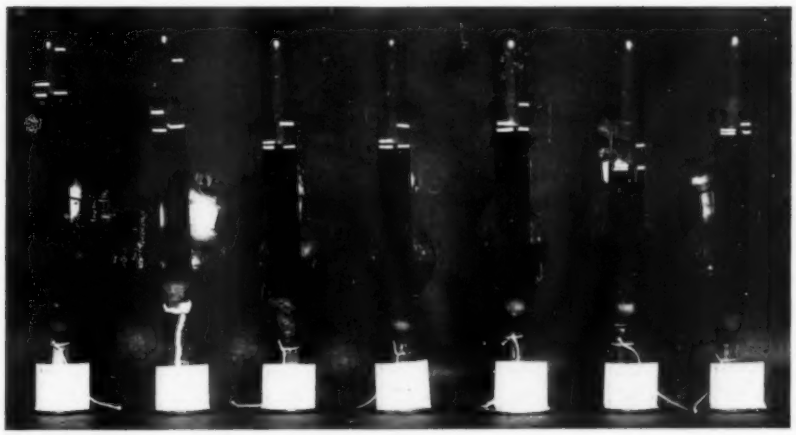
FIG. 3.—Reactions in the 1 per cent lactose bouillon not completely freed during its preparation from muscle-sugar. Slight gas-production except with B. paracolon.



Bacillus O. B. morbif. bovis. B. var. "Hatton." B. icteroides. B. coli (a).
B. paracolon. B. enteritidis. B. chol. suis. B. typhi mur. B. coli (b).

FIG. 4.—Typical reactions in 1 per cent lactose sugar-free bouillon.

FERMENTATION REACTIONS IN LACTOSE BOUILLON.



Bac. O. B. enterit. (Gärt.) B. chol. suis. B. typhi mur.
B. paracolon (Gwyn). B. var. "Hatton." B. icteroides.

FIG. 5.—Gas-production in sugar-free bouillon containing 1 per cent of dextrose.

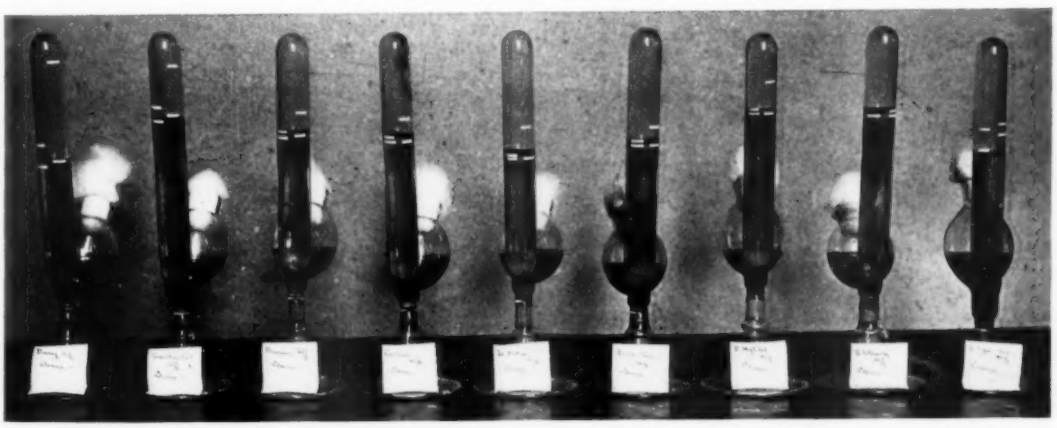


FIG. 6.—Gas-production in sugar-free bouillon containing 1 per cent of dextrose. For comparison with Fig 5. Showing relative slowness of gas-production with Bac. O and Gwyn's paracolon. The daily production of gas is indicated by labels.

FERMENTATION REACTIONS IN DEXTROSE BOUILLON.

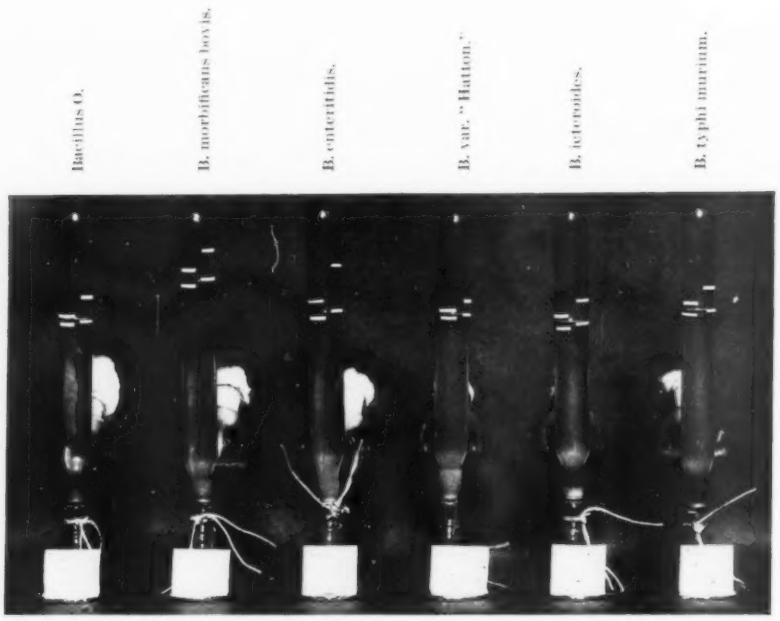


FIG. 7.—Reactions in sugar-free bouillon containing 1 per cent mannite.

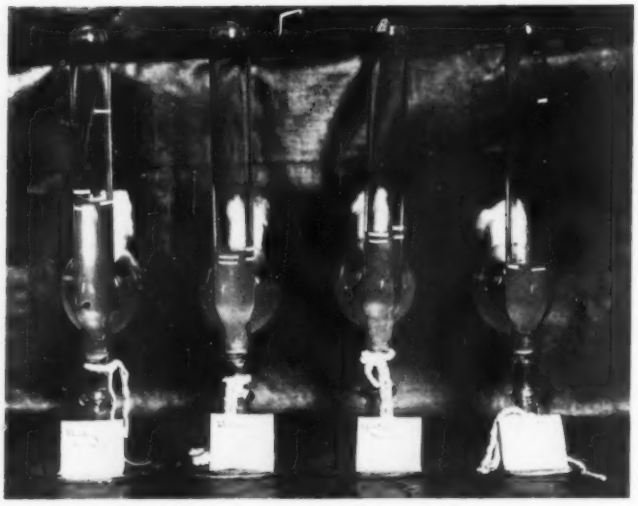


FIG. 8.—Reactions with 1 per cent mannite. Showing usual proportion of gas and rapidity of production with Bacillus O. The production of gas in the first twenty-four hours is usually small in comparison with the others unlike Fig. 7.

FERMENTATION REACTIONS IN MANNITE BOUILLON.

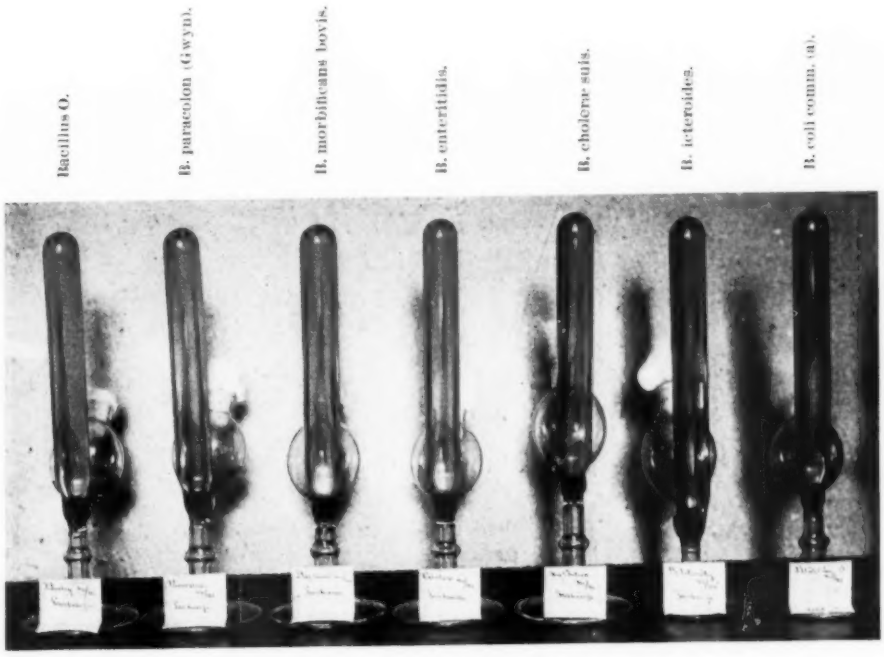


FIG. 9.—Reactions in sugar-free bouillon containing 1 per cent saccharose.

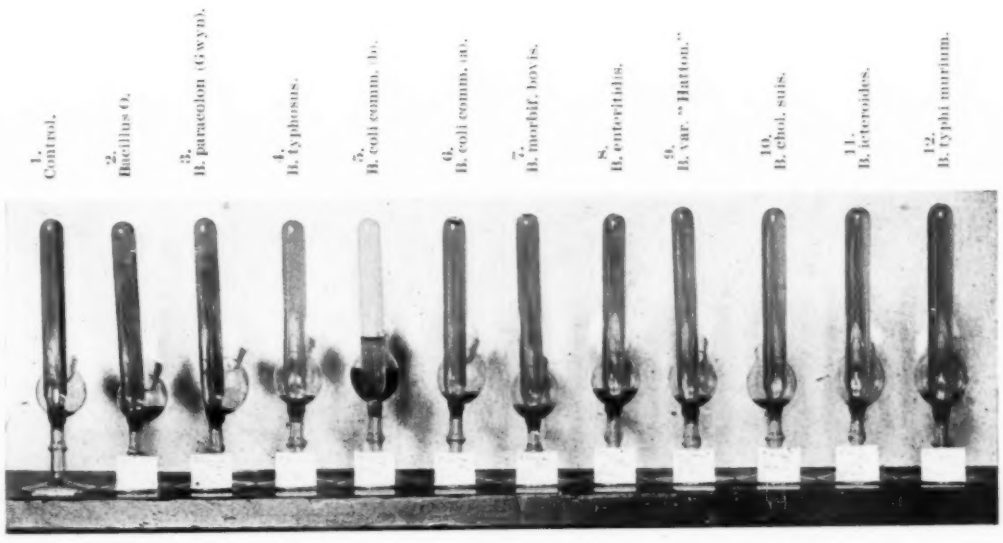


FIG. 10.—Reactions in 1 per cent litmus saccharose which had been partially converted during sterilization. Slight production of gas in tubes 2, 3, 6, 7, 9, 11, after 48 hours of incubation. At this time the litmus is completely reduced in the closed arm of the tubes containing the more rapidly growing organisms, 7, 8, 9, 10, 11, 12. Reductions of litmus in 2 and 3, slower in growth, are not complete till five days. The photograph shows the darker color of these tubes which have varied but little from the control.

FERMENTATION REACTIONS IN SACCHAROSE BOUILLON.

The mucous membrane of the duodenum in its upper 8 cm. was deeply congested, showing punctate hemorrhages, and the whole bowel and serosa over it were œdematous. The duodenal papilla was swollen and prominent and had two bright punctate points of hemorrhage on it.

Stained preparations of all the organs, bile and urine showed myriads of bacilli.

Cultures showed a pure septicæmia as follows: Heart-blood, spleen, kidney, liver, and gall-bladder, *B. ent.* (Gärtner), pure culture; duodenum and urine, *B. ent.* (Gärtner), and *B. coli com.* and an unidentified bacillus.

Sections of liver showed hepatic cells greatly swollen and having undergone a fatty change. No focal necroses.

BLACK AND WHITE RABBIT. Same weight.

Previously immunized to *B. typhosus*.

Preliminary serum reactions.

B. typh. 1–2000 positive.

B. ent. 1–10 positive and suggestive to 1–100.

Aug. 30. Corresponding inoculation. (Cf. WHITE RABBIT I, Aug. 30.)

Aug. 31. Lively.

Sept. 5. Died 3 P. M. Immediate autopsy. Blood taken just before death shows an agglutinative reac. toward *B. ent.* of 1–500.

Macroscop. lesions. Liver pale, soft, showing small yellowish areas of apparent necrosis.

Gall-bladder greatly distended, thin-walled and transparent. Bile, thin and watery with an abundant mucoid yellow precip. showing through the walls. Stained preparations from this fluid show masses of bacteria, chiefly in clumps, and desquamated goblet cells. No motile bacilli seen on hanging drop.

Duodenum negative. A few slightly injected points. Other organs were mac. negative.

Cultures. Heart-blood, sterile; spleen, few colonies of *B. Gärtner;* kidney, sterile; liver, few colonies of *B. Gärtner;* gall-bladder, multitude of colonies of *B. typhosus*, an unidentified Bac. and *B. Gärt.* (?).

Duodenum. B. pyocyaneus, B. coli com., unidentified bac. peptonizing milk.

Sections of liver show large areas of focal necrosis similar to those seen in WHITE RABBIT I.

From these last experiments we see that the normal control rabbit died of an acute general infection from *Bac. Enteritidis* with the usual characteristic lesions, especially referable to the eliminative system, namely, of the liver, gall-bladder and duodenum, from which organisms were obtained in greatest numbers. The rabbit (WHITE RABBIT I), which had apparently recovered from its infections with *Bacillus O* and *B. choleræ suis*, was killed at the same time, and it was found that no bacteria remained or could be found in the general circulation or organs, but an organism persisted in the gall-bladder which could be identified by serum reactions alone and was shown to be that of the most recent infection, namely, *B. enteritidis*.

The "typhoid" rabbit succumbed to his infection in six days with the characteristic lesions found after fatal inoculations with *B. chol. suis*, *B. icteroides* or other members of the group which are actively pathogenic. Necroses of the liver similar to those seen in this animal were found in WHITE RABBIT I when killed, and were probably due to the hog cholera rather than to the more recent Gärtner infection, else the control rabbit would have exhibited them.

These observations are too few in number to lead to any broad conclusions. They, nevertheless, are very suggestive of the possibility that immunization with one of these forms endows the animal with a certain degree of resistance toward infection with the others. Furthermore, an acquired serum reaction toward one form does not furnish agglutinative properties of equal degree toward other varieties even though they are so closely related as to be culturally indistinguishable. Thus agglutinative sera for individual forms may be obtained, by which means alone we can differentiate the organisms.

IN REVIEW.

A consideration of the cultural properties of the organism, *Bacillus O*, which has been dwelt upon at such length, demonstrates its close relationship to the definite and hardly recognized group of bacilli of the hog cholera or *B. enteritidis* of Gärtner type, which bacilli, having some characteristics peculiar to both the typhoid and colon groups, may be said to occupy a biological position intermediate to them. Whether the cultural characteristics of these organisms are but temporarily acquired, and whether they should merely be regarded as having a transient intermediary existence, may be a question of dispute; but, nevertheless, a certain distinct isolarity for these particular forms is demonstrable, and the definiteness of the serum reactions, pathogenicity, and perpetuation of cultural features justifies their installment in a separate group.*

The elaborate tables of Germano and Maurea,[25] of Tavel and Lanz, of Gilbert, Booker, Smith and others show what a variety of closely related bacillary forms of this family may be isolated from one source or another. In a recent study of the intestinal flora of dogs, Dr. Livingood and the writer † isolated about fifteen varieties of bacilli, chiefly of the colon and paracolon type, though several more intermediate forms were found, and on not a few occasions organisms indistinguishable from *B. typhosus*. It can thus be readily understood, if typical or allied forms of these various groups occupy at one time or another the alimentary tract, that during the course of fevers associated with intestinal lesions they may easily find their way into the portal circulation and cause an infection superimposed on that of the original disease. It has been shown, however, that colon, which is a permanent inhabitant of the lower intestine where these lesions are usually situated and consequently the most frequent secondary invader, is rarely found in infections beyond the confines of

* Cf. Flexner, Simon. Microorganisms. Twentieth Century Practice of Medicine, Vol. XVIII, p. 655, 1900.

[25] Germano and Maurea: Vergleichende Untersuchungen über Typhusbacillen und ähnliche Bakterien. Ziegler's Beiträge, Bd. XII, S. 495, 1893.

† Experimental and Surgical Notes upon the Bacteriology of the Upper Portion of the Intestinal Canal, etc. Contributions to the Science of Medicine, dedicated by his pupils to William H. Welch, p. 571, 1900.

the abdominal cavity. Gwyn's *paracolon* and *Bacillus O*, on the contrary, were isolated, one from the peripheral circulation and the other from a surface lesion, and consequently it is unlikely that they were secondary invaders. Furthermore, the patient's blood reacted strongly to these organisms and not to *B. typhosus*, and it is not improbable that they were the specific cause of the disease, which resembled clinically typhoid fever. For similar reasons the recovery of *B. icteroides* from the peripheral circulation of patients suffering with yellow fever would favor Sanarelli's view that it is the cause of a specific fever and not a secondary invader, as many are inclined to believe.

The individuals of this group of organisms spoken of as an intermediate group present a wide range of pathogenic activity toward man and animals, and though they can be distinguished by their response toward various specific sera, they are practically identical in their cultural reactions. Their chief distinguishing features from *B. coli* and *B. typhosus* may be given as follows:

Chief distinguishing features of the Eberth or typhoid, Gärtner or intermediate and Escherich or colon groups.

B. typhosus. An actively motile bacillus possessing as many as 14 flagella at times and having marked pathogenicity toward man though slight toward the lower animals. Reaction in milk is acid, with a very late (months) or no terminal alkalinity. The organism ferments glucose but not lactose and produces no gas from any carbohydrate medium. Under ordinary conditions of isolation there is no production of indol.

Fermentation reactions:

		Dextrose.	Lactose.	Saccharose.
	Total gas	0	0	0
	Aërobic:	Acid	Alkaline	Alkaline
Reactions:				
	Anaërobic:	Acid	Neutral	Neutral

Intermediate Group. B. Gärtner and *B. chol. suis* type. Bacilli with the morphology of *B. typhosus* and possessing an equal or greater number of flagellæ. Actively motile and in many cases having a distinct pathogenicity for both man and animals. Reaction in milk presents an early and terminal strong alkalinity in the presence of air, appearing after a transient acidity. Milk is never coagulated. They ferment glucose, with the production of gas, never lactose or saccharose. Under ordinary cultural conditions no indol is produced.

Fermentation reactions:

		Dextrose.	Lactose.	Saccharose.
	Total gas	1/2	0	0 or bubbles
	H/CO_2	2/1	0	0
	Aërobic:	Acid	Alkaline	Alkaline
Reactions:				
	Anaërobic:	Acid	Neutral	Neutral

Bacillus O and *B. paracolon* (Gwyn) may represent a subdivision of this group, being slower in their action on milk and growing less luxuriantly and more like *B. typhosus* in various fluid media and resembling it in their pathogenic action on animals.

B. coli and its many allied forms. A bacillus with sluggish motility possessing few flagellæ. Pathogenicity ordinarily is slight for man and animals. Growth on potato is abundant and colored. No alkalinization in aërobic growth. Reaction in milk is acid, invariably sufficient for coagulation. It ordinarily produces a large amount of indol. It ferments glucose and lactose. Saccharose may or may not be acted upon.

Fermentation reactions:

		Dextrose.	Lactose.	Saccharose, var. (a)	Saccharose, var. (b)
	Total gas	1/2	1/2	0	2/3 slow
	H/CO_2	2/1	2/1	0	3/2
	Aërobic:	Acid	Acid	Alkaline	Acid
Reactions:					
	Anaërobic;	Acid	Acid	Alkaline	Acid

CHARLES FREDERICK WIESENTHAL, MEDICINÆ PRACTICUS, THE FATHER OF THE MEDICAL PROFESSION OF BALTIMORE.*

By Eugene F. Cordell, M. D.

The first name of any importance in the medical history of Baltimore is that of Charles Frederick Wiesenthal, who was born in Prussia in 1726 and who settled in Baltimore in 1755. Family tradition asserts that he was "physician to Frederick the Great," but we possess no further details of his life in his native land. His familiarity with the organization of the medical department of the Prussian army, shown in his letters to the Maryland authorities during our Revolutionary War, lends some plausibility to the supposition that he may have been connected with that service during his early professional life. There is evidence to show that his family enjoyed a good social position, and his educational advantages must have been considerable.

It is uncertain whether he possessed a medical degree or not. Dr. Ezekiel John Dorsey, a pupil, in dedicating a thesis to him (Edinb., 1776) adds M. D. to his name, while another pupil, Dr. George Buchanan, in a similar dedication (Phila., 1789) gives the name only without title. He does not appear ever to have used the degree himself, and in the account of the establishment of the first Lutheran church in

* Read before the Johns Hopkins Historical Club, Feb. 12, 1900.

CHARLES F. WIESENTHAL.

REPRODUCED FROM A PENCIL SKETCH BY HIS SON ANDREW.

Baltimore, drawn up it is believed by himself, he is referred to as "Karl Fried. Wiesenthal, *Medicinæ Practicus.*" He makes no allusion to the subject in any of his letters, not even in that urging upon Andrew the importance of a degree.

There were not many inducements for an aspiring young physician in "Baltimore Town," when Dr. Wiesenthal settled here at the age of 29. It was then but a small village of some hundreds of inhabitants, with unpaved streets, with but one church and without a newspaper. Its chief thoroughfare, "Long," now Baltimore, St., was in a wretched condition—indeed at times impassible. Within five years certainly it had been enclosed by a picket fence and gates to protect it from Indians. Annapolis, on the other hand (where Upton Scott had settled two years before) was the seat of government, the centre of the fashion, influence and culture of the Province. But Baltimore, under the guiding genius of her "Romulus," as he was called—Dr. John Stevenson, a north Irishman—was even then looming up as the commercial metropolis of the state and it may be that he foresaw the future greatness which awaited it. Or he may have emigrated with a party of his countrymen, who selected Baltimore for a home, and from whom he was unwilling to be separated. Furthermore the country around was well settled and many of the landed proprietors were men of means, and able to compensate a physician liberally for his services.*

The summer that he arrived was signalized by the defeat of Braddock's army, an event that favored the growth of the town by deterring settlers from going westward. Shortly after his coming he married a lady of York, Pa., who bore him one son and three daughters. In 1771, he became naturalized. During the Revolution, he warmly espoused the cause of the patriots and his services and advice were of the greatest value to the state and country. In January, 1775, he was made a member of the Committee of Observation of Baltimore County and in December of the same year he received the appointment of superintendent of the manufacture of saltpetre for the state. In one of his letters he describes a journey made to some caves on the south branch of the Potomac, where an abundant supply of saltpetre was found. He published his method of manufacture of this substance in the Maryland Gazette, January 2d, 1776. On March 2d, 1776,† he was commissioned by the Council as Surgeon-Major of the 1st Maryland Battalion commanded by Col. Smallwood. In a letter to the Council of Safety, written at this time and still extant, he expresses his willingness to assist the cause to the extent of his power, strength and abilities and to go with the troops wherever they should be ordered. On the 12th of March, 1776, he published an appeal to the public "for linen rags & old sheeting for bandages." In the same year he was Medical Purveyor for the Maryland troops and Examiner of candidates for medical positions in the Service. In 1777, according to Quinan he was Surgeon-General of the Maryland troops, in which position he received a salary of "35 shillings a day & no rations." Dr. Wiesenthal does not appear to have served with the troops in the field, although he visited them in an official capacity in their camps. He seems to have had the general supervision of medical affairs in Baltimore, establishing and conducting a hospital, purchasing medical stores and instruments, examining candidates and rendering professional services to the soldiers and sailors in the service of the state at this point.

According to Mrs. M. E. Reigart, of Baltimore, his granddaughter (who is here present this evening), Dr. Wiesenthal resided first in the suburbs of the town in a stone house on the Clifton Road, which is still standing. At what time he moved to his Gay Street house does not appear, but there he lived for many years, occupying two adjoining 2½ story dwellings, the one to the north as a dwelling house, and the other as an office.* These houses were demolished about 25 years ago and a large shoe store was built on their site. The lot extended through from Gay to Frederick Street, and on the rear of it Dr. Wiesenthal erected buildings for his medical school and dissecting room. In these, which are still standing, he taught many students, among whom were Drs. William Augustus Dashiel, George Buchanan, Ezekiel John Dorsey, Andrew Wiesenthal and Frederick Dalcho.† In one of

* Gov. Sharpe reports, May 2, 1754, that the town has the appearance of the most prosperous one in the Province. Few, he says, except Germans, who are commonly the possessors of small sums of money, have settled and built in it. Letter quoted in *Trans. German Histor. Soc. of Md., 4th Ann. Report.*

† Quinan's Annals.

* Southeast corner of Gay and Fayette Streets, now Hill's Shoe Store. Fayette Street was not opened east of Gay until about 50 years ago, so that there was no corner there in Dr. Wiesenthal's day.

† Frederick Dalcho was born in London in 1770, his mother being Elizabeth Wiesenthal, a sister of Dr. C. F. Wiesenthal, and his father a distinguished officer under Frederick the Great, who having been severely wounded in battle had been permitted to retire to England for his health. Upon the death of his father, at the invitation of his uncle, young Dalcho came to Baltimore to prepare for the profession of medicine. He arrived in Baltimore in a sailing vessel on the 23d of May, 1787, "after a boisterous passage of 8 weeks." Here he obtained a good classical education, after which he devoted himself successfully to medical study including an extensive course of botany. He is said to have taken the degree of M. D. (his name is not included in the Catalogue of graduates of the University of Penna., but that catalogue is known to be very defective), and then to have obtained a commission in the medical department of the U. S. A. While stationed at Charleston, S. C., some difficulty arose between him and his fellow officers and he resigned (1799). He then entered on practice in Charleston and assisted in the establishment of a Botanic Garden. In 1807 he became coeditor of the Charleston Courier. He was also a very influential member of the Masonic body and later their Grand Chaplain. By request he published a work upon masonry which was adopted by the Order as an authority. In 1811 he became much interested in theology and a lay reader in the Episcopal Church. He was ordained Deacon in 1814 and Priest in 1818. In 1819 he was elected assistant minister of St. Michael's Church, Charleston, and continued with fidelity and acceptance to discharge the

his letters (June 5, 1787) he speaks of the dissection of a little negro boy which young Dalcho was at that moment engaged in making. It must have been here, too, that the body of the murderer Cassidy was being dissected in 1788 when the mob collected and put a forcible end to the procedure.*

Dr. Wiesenthal was a zealous Christian and it was largely through his efforts and liberality that the first Lutheran church was built in Baltimore.† He was also President and Physician to the German Society (1784).‡

Dr. Wiesenthal was not only a public-spirited and useful citizen, but he was also a learned and skilful physician; devoted to his profession and ever seeking to promote its highest interests. His letters to his son Andrew, who studied first in Philadelphia (1781-2) and later in London (1786-9), designed for his son's eye alone, display the purity of his character and the loftiness of his motives. They contain also many interesting items, advice and allusions upon which I shall proceed to draw in further illustration of my subject.§ In the first of the series dated Dec. 25, 1781, he says: "We receivd your Letters . . . in which I see your beginning to dissect yourself which pleases me and I insist that you continue to do the same manually in *propria persona*, and not being content with merely demonstrations after the Subject is prepard, as I want the practical part. it will lead you towards Operations and will make that part of Surgery more intelligible. I hope you will not be content with merely knowing the Situation of the Viscera, but will examine them minutely, their contents Vessels Ducts &c." . . . "I hear Doctor Shippen has a young Gentleman who prepares the Subjects for his Demonstration I would have you cultivate a strict friendship as far as his Morals will admit of (in which particular you know my firm Opinion) and frequently make Inquiries of the Doctor himself, who I hope is often with you himself & teaches."

In Dec., 1787, he expresses his satisfaction at Andrew's predilection for surgery, "in which the Quack must stand aside, whereas in Physic in this part of the World the most errant Quack if he has Assurance enough will often claim the preference & obtain it before the Man of real and true Abilities."

Here, from the first letter, is an allusion to Dr. Thomas Bond, of Philadelphia, the founder of the Pennsylvania Hospital and the first clinical lecturer in America: "I am glad you have introduc'd yourself to Doctor Bond though he may have some Oddities, you may nevertheless rely on this that his Acquaintance will be valuable to you both his Learning and Experience are unquestionable, and he moreover is very communicative and takes a Delight in instructing young Persons and that in proportion to their Diligence and Application you will therefore visit his Lectures frequently and freely apply to him to resolve Such things as may be obscure to you, he is a good Surgeon besides and may give you Some good hints in the hospital."

There are but few allusions to cases and operations. "Mr. Yates . . . was formerly to become a Surgeon but has quitted it . . . but although he quitted Surgery that did not quit him, he having a fistula in Ano and undergoing an operation in London unsuccessful he came over to Maryland and recomended to me by Governor Smallwood. I laid it open very extensively, and found it proceeding near the root of the penis up to that region between the bladder and the Rectum as well as along the Anus and to the Ischium where I was even apprehensive of a Caries, he having once had a Caries on the Tibia and lost a large Exfoliation, it moreover enters the Rectum as he says he has found some Excrements pass through the Wound and frequently flatus." . . . . . "I had last Summer a Child 4 Months old of M^{r} Will^{m} Buchanan's under my Care whose head bulgd out and distended every Suture it was taken with Convulsions. it was cured by applying blist^{rs} to the Spots for Some Weeks." He sends the report of a case in which "the quantity of matter issuing from a tumor no bigger than a walnut was nearly 3 pints." In Sept., 1788, he writes: "M^{r} Wolsenhome from St Mary^{s} City was this Morning with me for my Advice he came but lately from London has formerly had my Opinion in writing concerning some nervous Symptoms deriv'd from the Gout. he has consulted several eminent Physicians in London especially D^{r} Letsome & Heberden. he show'd this Letter I mean Heberden my Opinion in writing concerning the Complaint &

duties of that position until declining health compelled him to seek repose. His vestry declined his offer of resignation but gave him an indefinite leave of absence with continuance of his salary. He died Nov., 24, 1836, aged 76. His principal work was a history of the P. E. Church in S. C. during the colonial period, which is considered an authority upon that subject. He wrote other religious works, sermons and essays, and edited a church paper. A monument was erected over his grave by the vestry of the church. He was about 5½ feet high and well proportioned. His manners were genial, his intellect vigorous and well cultivated and he was a general favorite in the community. See *Annals of American Episcopal Pulpit*. By Wm. B. Sprague, N. Y. 1859.

* Griffith's Annals.

† This church stood on the south side of "Fish" (Saratoga) St., near "Bridge" (Gay) St., and near the site of the present Bethel African M. E. Church. The first building was erected in 1762 and was an unpretentious wooden structure used also as a schoolhouse. It stood on a high and steep hill. About 1771 the excavations for streets in the vicinity, made the building insecure and shortly after it was pulled down, the material sold and the hill leveled. A brick building was erected on the same site (Quinan says in 1773). "After twelve years," to provide further accommodations for the growing congregation, an addition was made to it. The late Rev. Dr. H. Scheib recollected this ugly structure with its organ. It was entered by a high stairway at the side. In 1808 it was sold to the African church and a large church was built on ground further to the north, the present Zion Independent Lutheran Church. Dr. W. was a liberal contributor to the early church; he was an elder of the congregation and his name comes always at the head of the lists of members. See *The Zion Church of the City of Baltimore*, by Rev. H. Scheib, *2d Ann. Rept. Germ. Hist. Soc. of Md.*

‡ Quinan, *op. cit.*

§ They are closely written in a fine, neat hand. They are closely copied in the extracts here given.

Treatment which being approv'd of by the Doctor furnished some little Stoff for my Vanity." In an earlier letter to the Council of Safety (*Md. Archives*, Dec. 8, 1776) to which my attention has been called by Dr. Jackson Piper, he describes a curious case of "Eresypelas" in a soldier, due to taking cold, and involving the entire body "from head to foot," "the Vesications common in that Disorder displaying a humour so sharp that in a few days he was all over deprivd of his skin." He had likewise lost his eyesight and his life had been saved with the utmost difficulty. The doctor regarded the blindness as incurable. He advises Andrew to study to become skilful in surgical operations especially lithotomy and "extraction" of cataract. He refers to the great success of Dr. Tyler, a young physician of Frederick who had made considerable reputation in "couching the cataract." He tells him to study closely the action of drugs and to make himself acquainted with all new discoveries.

He was very anxious for Andrew to take a degree and expresses regret that the latter had not gone to Edinburgh to study instead of to London. He longs to see something in print "over the name of A. Wiesenthal that may meet the approbation of the learned." He asks what is to be the theme of his inaugural essay? in what language shall it appear? Is he sufficiently master of the Latin to hold a public disputation? In Leyden, at least, a public disputation is not demanded—perhaps at Rheims the same is the case. Would that he were with him to assist with advice and counsel! He sends A. from time to time copious notes of cases and opinions on various medical subjects, which he urges him to put into shape for a thesis or for publication in some journal. Oct. 14, 1787, he writes: "I have sent you various Cases in Physic and will consider of some more, and I think I will likewise send you some of my Theoretical Opinions which you may be probably able to elaborate something farther and should it be worth the Notice of some of your friends it might be perhaps worth while to have it published, for this is Truth that a great many more silly things have been published than what we should." In Nov., 1788, he tells him that a diploma is indispensable and suggests that he might obtain one in some institution without residence, or an honorary one. "Doct. Brown the great opposer to Dr Cullen's Doctrine and who now resides in London and as common Report says even in the Fleet's prison where he lectures, has wrote many a young Students Thesis on which he obtaind his Diploma blindfold."

The substantials of life are not forgotten. The Christmas letter of 1781 already spoken of concludes: "We congratulate you to these Christmas holidays and wish you had one of our very good min'ed pyes." In Oct., 1787, he sends Andrew a box of "hommany Beans & Sweetmeats." In another letter: "Mr. Yates sails on the Willing Tom next Week and I hope he will be able to take the Geese with him but I am allmost afraid we are too late. Mama I apprehend by wanting to extend her bounties will be the Cause of your getting none." The next day—in a postscript—"My Suggestions are but too true, the Willing Tom is sailing from Patowmack and the smoaking the Geese requiring a little more [time] lay till at last the S(c)hooner saild from Annapolis by which all remaining Stores were sent and Mr Yates going by Land obligd us to postpone it to another Opportunity which we hope will soon happen."

Dr. W. was very anxious to have a law passed for the regulation of medical practice in the state and headed a movement with that object in view. The prevalence of quackery, the low standard of medical training and the reprehensible conduct of many physicians in good standing, made an organization of the profession and a regulation a necessity. On Sept. 12, 1788, he writes thus: "To rescue the Dignity of Physic from that horrid State into which it is plungd within these few years and most especially since my Sickness will require a Herculean Labour, and it will fall in some Maisure to your Lot to undertake the laborious Task." After a full and public discussion of the matter in the town paper, a meeting was called for Nov. 27, 1788, the call being signed by himself. At this meeting which was most probably held at his house, he was chosen chairman. There is mention of it in a letter dated Nov. 28, 1788: "We are just about procuring a Medical Regulation in a little more earnest than heretofore, it nevertheless meets with some underhand jalousy and what amazes me it comes from Doct. B . . . we have had 3 meetings he has had allways written Invitations and each Time evaded it. The reason we only guess at. Last Nights meeting it was proposed for the Sake of Order and to have jointly more Weight to organize ourselves into a Society under Rules. I was unanimously nominated President and Mr Frederick for Clark, so that he has now an office." The plan which was then framed embraced the entire state in its operations and was similar in its features to the Charter of the Medical and Chirurgical Faculty adopted eleven years later. But for Dr. Wiesenthal's ill-health and death the following spring, there is little doubt that he and his associates would have succeeded in their object, and thus have anticipated by ten years the founding of the Medical and Chirurgical Faculty.

Dr. Wiesenthal almost idolized his son Andrew—his only son. His letters abound with the most endearing expressions, as this: "so tender a father as I am who makes his Sons welfare his only happiness in this World," and he lavished his money freely in giving him the best opportunities then available for education. In Sept., 1788, he estimates that he has supplied Andrew with nearly £450 sterling—"a pretty Modest Sum in these dreadful Times," he adds. Moreover we must remember that Andrew lived with his aunt during his stay in London, and that the above amount did not include his books, instruments, medicines and the passage money home, which were still to be provided. He chides him mildly on one or two occasions and refers to a letter of A.'s headed "*sans six sous*," which seems to have worried him a great deal.

The following pathetic passage occurs in a letter of No-

vember 28, 1788: "I for my part am allready discarded and laid up like an old Man of Warship. although the Shafts of Jalousy are still continued to be let off against me as if they dreaded my returning to my usual Strengt again nay I veryly believe, they will hate my very Memory ten Years after my having returned to Dust, and be afraid and Jalous of me (horrid indeed!) if I reflect that at all Times I have acted up to the Dignity of the Profession, have disdaind all mean Empyrical Methods, because I had no Occasion I think that I ought to be respected as a father and Supporter of the Profession and be treated friendly." In another letter about the same time he writes: "I find no remedy now in the late Evening of my Life as to prostrate myself before the Throne of the Allmighty and expect in the other World that which this has denied me."

Towards the last, Dr. Wiesenthal, who was of a highly nervous temperament, suffered greatly from hypochondria. Every circumstance became irksome to him and he sought and found relief from his despondency in the tinctura thebaica which he supplemented with the liquor anodyni Hoffmanni. The dose which he took of the former was not extreme, not exceeding, according to his statement, 40 to 45 drops.

His last letters show that he was failing. Sept. 12, 1788, he writes: "My health, my dear son, is very precarious and being in my grand Climacteric, the 63d year of my Age I find myself declining every day." Although he lingered on to the spring of 1789, his eager longing to see his son before he died was not gratified. There is something inexpressibly sad to see this good old father sinking into the grave, hoping day by day for the return of his son beyond the sea and with his life lit up by that one thought alone.

The following is the notice of Dr. Wiesenthal's death taken from the *Maryland Journal and Baltimore Advertiser* of June 2, 1789: "The shaft he so often warded from others has pierced him at last. Yesterday morning about half past seven o'clock departed this life Dr. Charles Frederick Wiesenthal, in the 63d year of his age after having practiced in this town for 34 years. If the strictest attention in his profession which humanity could excite & that success which might be expected from superior medical abilities improved in an uncommon measure by reason & observation deserve to be remembered, the tears of gratitude must flow in sorrowful profusion. He is gone! & the pain of reflection is the more heightened because it is at the time when he was in daily expectation of the return of an absent & only son whose virtues & abilities are beloved & admired by all who know him."

Dr. Wiesenthal's picture suggests a large, fine looking dignified man with a German type of countenance. He was generous and hospitable and particularly kind to the poor, often remitting his charges against them when they seemed unable to meet them.* His dress is described as follows: "a scarlet cloak, three cornered hat, blue velvet coat with gold buttons & buff facings, buff vest, lace ruffled shirt, knee breeches, stockings, shoe buckles, plain white cravat surrounding neck, wig & cue tied with a black ribbon." He was the first physician in Baltimore to drive a four-wheeled carriage. On this was inscribed his crest & motto—"a horse's head bridled & bitted with two crossed arrows beneath & the words Premium Virtutis."

Dr. Wiesenthal's remains were interred in the burial ground attached to the church, but were afterwards removed to Loudon Park Cemetery. No tombstone was ever erected over them. Andrew died in 1798, at the early age of 36, leaving a son Thomas Van Dyke Wiesenthal, who became a surgeon in the U. S. N. There is only one person now living bearing the name of Wiesenthal, an aged single lady residing in Boston, but whose present residence we have not been able to find.

One of Dr. Wiesenthal's pupils in dedicating his graduation thesis to him, speaks of his "great professional skill, his rare & singular virtues & his nobility of character";† another compares his position in Baltimore to that of Sydenham in London.‡ I venture to think that after what we have heard this evening we shall not consider him unworthy of the further title—one which he so much coveted—"Father of the Medical Profession of Baltimore."

[In connection with the above paper, there were shown a pencil portrait, drawn by his son Andrew, his crest and motto, and a photograph of his medical school, still standing.]

Authorities consulted:

Letters of Dr. C. F. Wiesenthal, MS.
Quinan's Annals.
Maryland Archives.
Newspapers of Baltimore and Annapolis.
Griffith's Annals.
Rev. Dr. H. Scheib's Article (Germ. Histor. Soc. Pubs.).
Family Tradition (Mrs. M. E. Reigart).

* "When patients came to settle bills, if poor, he would look in his books and say: 'I don't find anything against you.'"—Mrs. Reigart.

† *Dissertatio Inauguralis de Nutritione.* Ezekiel John Dorsey, Edinb., 1776.

‡ *Vir Venerabilis, Carolus Fredericus Wiesenthal, rei medicae apud Baltimorienses cultor felicissimus, qui ob magnam omnium quae medicinam spectant, notitiam, non minoris ibi quam Sydenhamius olim apud Britannos fuit aestimatus, penditur.* Inaugural Thesis of Dr. George Buchanan. Univ. Pa., 1789.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XI is now in progress. The subscription price is $1.00 per year. The set of ten volumes will be sold for $20.00.

Dr. Wiesenthal's Medical School, the first established in Baltimore. We do not know when it was opened, but there are grounds for conjecturing that it was between 1760 and 1770. In February, 1774, Dr. W. A. Dashiell defends the views of his preceptor (C. F. W.) in the newspaper, a controversy having arisen between the latter and Dr. Ephraim Howard, concerning the use of venesection in a case of pneumonia, and in his inaugural thesis at the University of Edinburgh, 1776, Dr. E. J. Dorsey speaks of Dr. W. as having taught him the elements of medicine. The view was taken from a second-story window of house northeast corner of Frederick and Fayette streets, and one is looking a little south of west. The street before us is Fayette, between Gay and Frederick. In the distance one sees over the tops of the houses, the cross of Church of the Messiah (P. E., on Gay street). In the centre of the square is the long two-story schoolhouse containing the sign "Hill's Hand-made Shoes". The smaller two-story building, at the nearer end of the square, also stood in Dr. W.'s day, and is believed to have been his dissecting-room. At the further corner of the square is Hill's shoe-store, built about twenty-five years ago, on the site of Dr. W.'s residence. Fayette street, formerly "East Street," was not opened between Gay and Frederick until about fifty years ago, and the doors and windows of the school-house on that side must have been made at that time. The stone steps at the side used to be at the front entrance. The old lady is Mrs. Reigart, granddaughter, and the young gentleman to her left, at the edge of the pavement, is Mr. John Milton Griffith, great-great-grandson of Dr. W. Mrs. Reigart lives at 216 Girard avenue, and is over 82 years of age. Behind them is the writer of this sketch. After his father's death in 1789, Andrew taught here until his death, in 1798. Shortly after the latter event, the house, which was then 40 N. Gay Street, passed out of the possession of the family. It is now unoccupied. About fifty years ago it was used by Mr. McMullan (who is still living) as a furniture storeroom. Mrs. Reigart is the daughter of Julianna Susanna Beneowsky Wiesenthal, "the mischievous little Julianna, the pretty little babbler," of the letters, born four years before Dr. W.'s death and named from her godmother, Countess Beneowsky, sister of Mr. Messonnier, the importing merchant of Baltimore, who married Dr. W.'s daughter Elizabeth. To be absolutely certain that there was no mistake, the writer took Mrs. R. (who is a very intelligent person, with senses and faculties all good) to see the premises, which we inspected thoroughly. Although she never lived there, she has perfect recollection of the place, which she has often visited before. She says that her mother's nurse—a white woman—lived to an advanced age, and often talked to her of her grandfather and his family, and pointed to the building as her grandfather's school. There is, therefore, no question about its identity.

I. PRIMARY CARCINOMA OF THE APPENDIX VERMIFORMIS; II. CARCINOMA OF THE APPENDIX SECONDARY TO CARCINOMA OF THE OVARIES.

BY ELIZABETH HURDON, M. D.,

Assistant in Gynecology, Johns Hopkins University.

New growths of the vermiform appendix are so unusual and hitherto have received so little attention that each case is worthy of being recorded. The following cases, one of primary origin, the other secondary to an ovarian tumor, have recently occurred in the service of Dr. Kelly, to whom I am indebted for the privilege of making this report. Apart from its rarity the first case is of interest on account of the early stage in which it was discovered owing to the routine examination of the abdominal viscera made in all cases of abdominal section. The second case was also detected by this general examination.

In the literature there are references to ten cases of carcinoma originating in this organ. Of these, however, only the three cases in which the diagnosis was confirmed by a microscopic examination can be accepted as well established. These were shown to be of the usual type of carcinoma of the intestines. In two cases the growth had penetrated the abdominal walls appearing externally as large crater-like ulcers with thick irregular margins.

In Thiersch's case, reported by Bejer, the extension had taken place along a sinus which had persisted for three and one-half years after the opening of a large pus-sac in the right iliac fossa. On partly removing the external mass a finger-thick cord was disclosed which extended down into the peritoneal cavity. This proved to be the vermiform appendix, and in the cecum a tumor the size of a walnut could be felt surrounding the orifice of the appendix.

The writer calls especial attention to the early formation of adhesions and infiltration of the abdominal wall and to the absence of intestinal symptoms. He is of the opinion that the growth began in the apex of the appendix and slowly extended along the mucosa to the cecum.

In the case described by Kolaczeck the right lumbar region presented a deep ulceration, at the base of which was the denuded os ilii. At autopsy the appendix was found to be destroyed by a tumor which had invaded the walls of the cecum, and also the surrounding cellular tissue and the psoas muscle.

Morse and Daumic report a case occurring in a woman 50 years old who had died of heart-disease. The vermiform appendix floated free in the peritoneal cavity, was 4 cm. long, 4.5 cm. in circum. and cylindrical in shape. On transverse section the muscular layers could be seen enclosing a hard mass within which was a narrow canal opening into the cecum. The tumor did not project at all into the cecum and was limited to the appendix. Histological examination showed the muscular coats for the most part normal, but in places separated by small islands of epithelial cells. The peritoneal coat was normal. In the central part of the tumor near the canal were seen remains of the mucosa and of Lieberkühn's glands. The latter had for the most part undergone cancerous transformation and were probably the origin of the neoplasm. No other growth was found.

Carcinomata occurring in the vermiform appendix are of the two varieties commonly observed in growths affecting the alimentary canal, namely, colloid carcinoma and adenocarcinoma with glands resembling proliferating glands of Lieberkühn. An unusually large proportion of the cases occurring in the appendix if we accept the diagnosis made from the gross specimen are of the colloid type.

The clinical notes on the present case are briefly as follows:

Gyn. No. 6646. Mrs. G. Age 24. Married 9 years. II para. The oldest child 8 years, the youngest 3 years old. 2 miscarriages, the first six years ago, the last in August, '98. Her family history is unimportant, with the exception that one brother died at the age of 18 after amputation of the leg for a "cancer."

The patient had always enjoyed excellent health until the birth of her first child. At varying intervals thereafter she suffered pain in the lower part of the abdomen and back. The pain was described as aching or dragging in character and was most severe the week preceding and following menstruation. Last spring the patient had a fall and afterwards the pain which previously had been limited to the pelvis became more marked higher up in the right iliac fossa and was associated with constant aching in the right lumbar region. This was ascribed by her physician to a floating kidney which was found to be present. Her appetite failed and at times she suffered from nausea and vomiting.

On palpation the abdomen was non-resistant, and there was no tenderness in either iliac fossa. The right kidney was palpable and slightly movable; on bimanual examination the uterus was found in acute retroflexion and its mobility was restricted. Further examination was negative.

Operation by Dr. Kelly, Feb. 21st, 1899. Release of pelvic adhesions; suspension of the uterus; removal of the vermiform appendix.

The uterus was found retroflexed and bound down by a few light adhesions. The tubes also presented a few adhesions somewhat stronger on the right than on the left side. Apart from these adhesions the tubes were perfectly normal and no cause for the pelvic peritonitis could be discovered until on looking for the appendix it was found hanging down into the pelvis over the right infundibulo-pelvic ligament and enveloped in dense vascular adhesions. A shortened mesentery caused the outer third to redouble on the inner portion, and at the point of flexion there appeared to be a foreign body in the canal.

The appendix was amputated close to the cecum, the uterus

and tubes freed from adhesions and the uterus suspended. The abdomen was then closed in the usual way.

The patient made an uneventful recovery and was discharged March 16th. In a letter written Dec., '99, she stated that she had gained twenty-three pounds and her general health was excellent. She suffered, however, from some discomfort in the right lumbar region, probably owing to the movable kidney.

Pathological report: Gyn. path. No. 2854. The appendix is 10 cm. long. At the junction of the middle with the outer third it is slightly flexed and held in this position by broad velamentous adhesions. The proximal end is practically normal but the part beyond the flexion is distended, having a diameter of 12 mm. and contains a soft concretion of about the size and shape of a date-stone. The walls here are thinned, averaging not more than 1 mm. Their internal surface is smooth. Joining the distended extremity to the normal inner half of the appendix is an intermediary portion about 1.5 cm. long, of firm consistency. Previous to removal this was supposed to contain a concretion but on transverse section it is seen that the lumen is practically obliterated by a small oval swelling which impinges upon the canal so that merely a small crescentic slit remains. This is displaced toward the inferior border of the appendix by the tumor which encroaches from above. To the naked eye this minute tumor appears to be about 1 cm. long, and 5 mm. in its greatest thickness. Its cut surface presents a whitish dense appearance and is partly homogeneous, partly finely striated. It is enclosed by the muscular coats into which its external margin imperceptibly merges.

Histological Examination.—In a transverse section through the portion of the appendix occupied by the new growth it is seen that all its coats to a greater or less extent are infiltrated with epithelial cells in the form of nests or cylinder-like processes. The muscular coats are not thickened and the epithelial processes which here are slender and cord-like invade the interstitial connective tissue while the muscle bundles remain unaffected. The epithelial proliferation is most evident in the mucous and submucous layers, which are markedly thickened, forming a rounded prominence which encroaches upon the central canal. The cells in this portion are arranged in oval or irregular masses, or in parallel columns consisting of three, four or more rows of cells. The intervening stroma is scanty and indeed the epithelial masses are sometimes directly contiguous. In the center of the column of cells a narrow central canal is sometimes faintly visible, and in the larger masses the cells are now and then seen to be disposed in little circles which may present a minute central lumen. Extending downward from the surface of the mucosa there are a few normal glands of Lieberkühn. Others which are found here and there between the cancer nests show beginning proliferation and alteration of the character of the epithelial cells and are undergoing early carcinomatous changes. The starting point of the growth has probably been in the area included between points p. and c., Figure 2, as here all the glands have been replaced by masses of tumor cells.

The surface epithelium of the mucosa has not taken part in the tumor-formation and is intact, though where the growth impinges upon the canal the cells are flattened. The mucosa lining the opposite side is attenuated and its glands shallow and few in number but the epithelial cells exhibit no tendency to become proliferated and are unaltered in appearance. The lymph-nodes have disappeared. The submucosa is scanty. Both circular and longitudinal muscular coats are of normal thickness.

On higher magnification the tumor-cells are seen to be fairly uniform, the peripheral layer of the nests consisting of low columnar, the central mass of oval cells. Where the minute lumina are present in the cell masses they are also lined with low columnar cells. The cell nuclei are oval or spherical and are vesicular. Their chromatin is finely granular. There are, however, various large cells containing deeply stained hyperchromatic nuclei which are coarsely granular. Mitotic figures exhibiting the different stages of cell-division are moderately numerous.

The invasion of the muscular and peritoneal coats is associated with but little inflammatory reaction, but the mucous and submucous layers show a marked leucocytic infiltration and it is noteworthy that a considerable proportion of the infiltrating cells are eosinophiles.

In the superior segment of the appendix, that is, the portion farthest from the mesenteric attachment, the growth has penetrated all its coats extending to the peritoneum, which contains many large round or oval cell-nests, d. Fig. 2, but the inferior segment has apparently been invaded only in the circular muscular tunic where a few strands of epithelium extend almost entirely around, running parallel with the muscle fibers.

The various coats of the cystic extremity of the appendix though thinned out preserve their normal proportions. Its inner surface is smooth and even, and its epithelial lining intact. The glands are diminished in number and shallow but otherwise unaltered; the stroma scanty and the lymph follicles atrophic and widely separated from one another.

The cecal half of the diverticulum is normal in all respects.

The first cause of the formation of carcinoma affecting any organ remains to be discovered, but the presence in this case of the fecal matter suggests an important question as to the etiological significance of foreign bodies in the development of tumors. The occurrence of new growths of the bile-passages and kidneys with calculi intimately associated has frequently been observed and a few tumors of the appendix have been described which had developed around foreign bodies as their centers. An instance described by Lafforgue is a small lipoma situated in the wall of the appendix which contains a small concretion in its center.

Gilford reported a case of sarcoma surrounding a concretion in the appendix, the growth having apparently resulted from

FIG. 1. Primary carcinoma of the appendix. The position and caliber of the canal are indicated by the dotted lines beginning at *a* and extending to the apex. *d* shows the dilated extremity. Between *b* and *c* is an indurated portion gradually merging into the normal.

The flexion is not so acute as before cutting the mesentery.

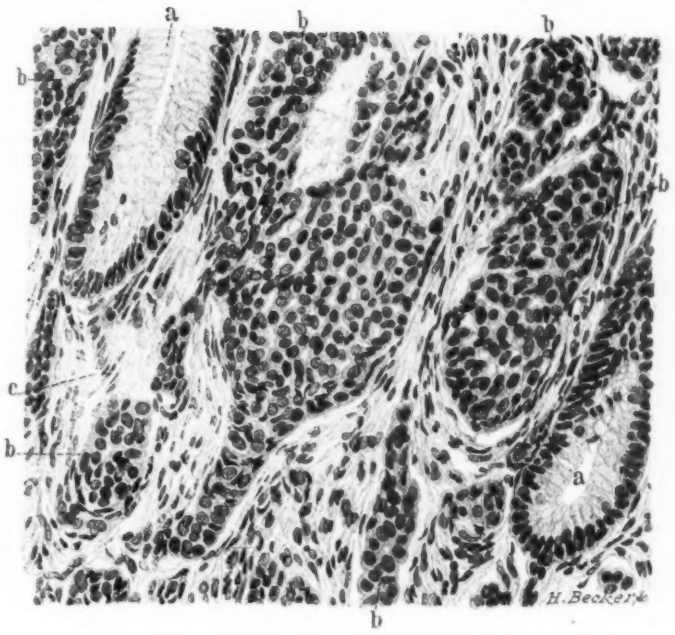


FIG. 3. A higher magnification of a small area in Fig. 2, carcinoma of the appendix (350 diameters). Two glands of Lieberkühn are seen at *a*, and masses of carcinoma cells at *b*; *c* indicates the stroma.

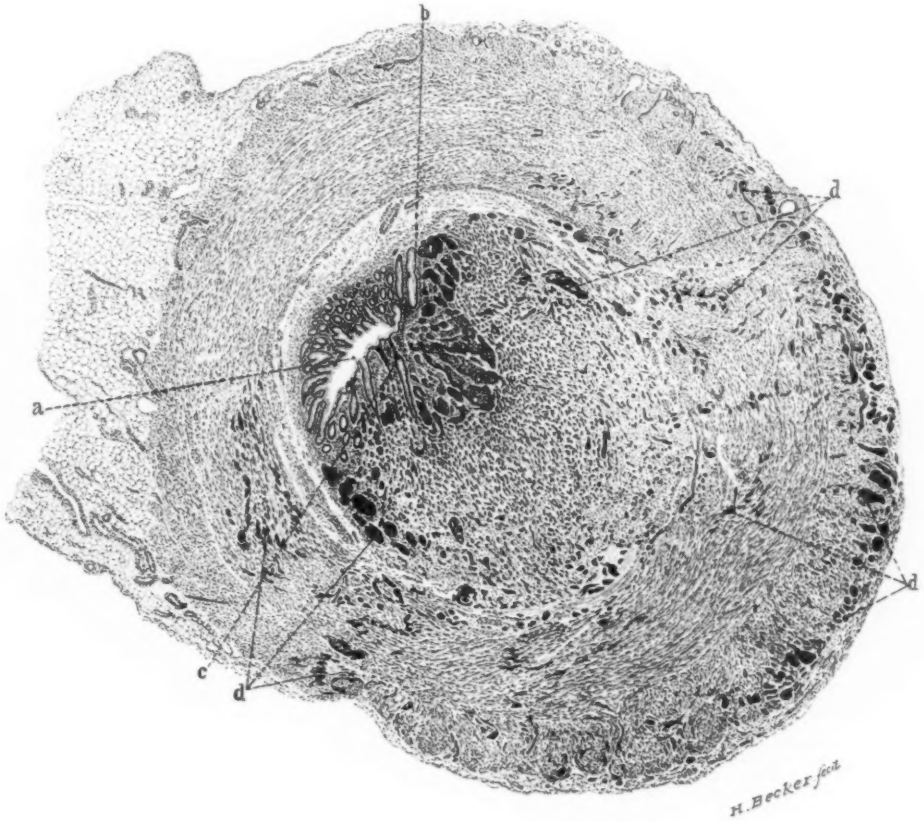


FIG. 2. Transverse section of carcinoma of the appendix (15 diameters). The canal of the appendix is seen at *a*. On the left side the mucosa and submucosa are practically normal; a few strands of deeply stained tumor cells are present in the circular muscular coat; the longitudinal muscle and mesentery are normal. On the right between *b* and *c* the glands of Lieberkühn have been replaced by the neoplasm, and islands of tumor cells, *d*, are scattered throughout the remaining coats.

a previous appendicitis. The tumor was removed with a portion of ileum and colon to which it was adherent and the patient made a good recovery. On cutting open the tumor three or four small collections of pus were laid open and in one near the middle of the mass was a fecal concretion twice the size of a cherry-stone. A probe passed into this cavity passed down the appendix vermiformis into the cecum. The microscope showed principally large oval and spindle-shaped cells, and the growth was considered to be an undoubted sarcoma. A small nodule was also excised from the right psoas.

In the cases of carcinoma of the appendix reported in the literature one writer mentions that a fecal concretion was present in the dilated extremity, the growth in this case affecting the cecal end. In our case the foreign matter is of softish consistency and there is no evidence of irritation of the epithelium lining the canal at any point. It is conceivable, however, that the presence of the body with the impossibility of expulsion due to the kink has in some way incited the atypical glandular proliferation.

Several of the cases quoted gave histories of attacks of acute appendicitis occurring some years before the discovery of the cancer.

DIAGNOSIS.—The difficulty of diagnosis in carcinoma of the appendix is indicated in the histories of the cases quoted above and is owing to the absence of distinctive symptoms in the early stages. Our attention is first directed to the iliac region by the onset of pain and the presence of tumefaction, and when these are manifest the growth is usually well advanced. As a rule there is no interference with the digestive function until the growth has invaded the cecum or the large or small intestine. This was observed in only two cases late in the course of the disease. The most constant symptom is the presence of a dull pain of a not severe type affecting the right iliac region and extending to the right groin and thigh. On making a physical examination a firm mass is found occupying the position of the appendix vermiformis. This is usually cylindrical and before adhesions have formed is freely movable within a limited radius. The appendix, however, may be small and nodulated as in the cases of scirrhous carcinoma and is then hardly to be distinguished from a calculous appendix. The diseases for which carcinomatous appendix is most apt to be mistaken are: cyst of the appendix, calculi, tuberculosis of the so-called neoplastic form, impacted feces in the cecum or small intestine. Floating kidney was diagnosed in the case of sarcoma of the appendix recorded by Gilford.

In many instances only an exploratory section will enable one to make a positive diagnosis.

PROGNOSIS.—If we should consider the prognosis of carcinoma of the vermiform appendix from the standpoint of the outcome in the cases reported it would be rendered extremely grave. It must be remembered, however, that the majority of these cases were observed in an early time and before the period in which operative interference began to be so generally employed. Moreover in one case death was due entirely to an intercurrent affection and in three other cases we do not know that the growth was in any way responsible for the fatal termination. On the other hand, however, the absence of functional symptoms and the little pain excited by the presence of the growth may cause it to be overlooked until the surrounding tissue has been invaded or until rupture occurs, and in the latter case the ensuing general peritonitis is itself attended with serious consequences. In the present time when the vague pains accompanying mild affections of the appendix are more carefully investigated and when operative interference is more generally employed for the relief of such cases the prognosis in carcinoma is rendered more favorable as it is for this class of cases that early carcinoma is liable to be mistaken.

TREATMENT.—There is little to be added regarding the treatment in cases of carcinoma, as when the symptoms or the results of the physical examination warrant the assumption that the appendix is diseased, the safest course is to perform an exploratory section, and if the suspicion is verified, to remove the appendix. If the appendix is found to be the seat of a new growth in order to insure its complete removal the head of the colon should be resected and should the growth have visibly extended beyond the appendix a more extensive resection may be indicated. In cases still further advanced and involving the abdominal fasciæ a radical cure can scarcely be expected and the patient receives little benefit from an incomplete removal of the tumor.

SECONDARY CARCINOMA OF THE APPENDIX.—Secondary carcinoma of the appendix is of interest chiefly from the scientific standpoint, since clinically, as it gives rise to no symptoms or to none that are characteristic, its presence is masked by the primary tumor. Moreover, if detected its removal does little to stay the progress of the disease. Metastatic carcinomatous growths in the appendix appear to be almost as rare as the primary cases, most of the secondary growths consisting of direct extensions from the cecum. The most frequent seat of the original tumor appears to be in the ovaries, the stomach or other portion of the digestive tract, or the uterus. The growth in the appendix corresponds in structure to the original tumor.

The case I have to report was discovered at operation for removal of a large ovarian tumor, and at the same time it was found that the pyloric end of the stomach was also the seat of a new growth.

Gyn. No. 5262. Mrs. S., age 57 years, was admitted to the gynecological service complaining of an abdominal tumor associated with some pain in the lower abdomen and a slight sanious discharge of about six months' duration. She was a healthy-looking woman, her appetite was good but she suffered from slight indigestion and chronic constipation. Further than this her history is unimportant.

Operation by Dr. Kelly.—Removal of both ovaries and tubes and the vermiform appendix.

The left ovary was transformed into a large oval tumor of remarkably dense structure. On microscopic examination this was found to consist of small round or oval glands imbedded in a dense cellular connective-tissue stroma. The glands were lined with low columnar or flattened epithelial cells with protoplasm stained deeply with eosin and containing large nuclei of variable shape and intensity of color. The epithelium was mostly disposed in one layer but occasionally two or three layers were seen.

The remaining pelvic organs appeared normal with the exception that the mesosalpinx of each side was thickened and the peritoneal surfaces of the broad ligaments and uterus were studded with a few small flat white nodules. One of these was excised and examined under the microscope showing only fibrous tissue but doubtless further sections would have revealed their carcinomatous nature. Microscopic examination of the right ovary showed that though not enlarged it was also invaded by the new growth which was limited to two well-defined areas immediately beneath the albuginea, and a small area in the hilus.

The vermiform appendix was found to be thickened, nodular and very rigid in its outer half, the cecal half being normal. The mesenteriolum was indurated. On cutting open the appendix its outer third was found to be slightly distended, containing a small fecal concretion. Internally to this there is a nodular enlargement 1 cm. in diameter formed by the general thickening of all its coats. The lumen here is constricted. The proximal half is of normal caliber.

Histologically, excepting in the thickened median portion of the appendix, nothing of importance is noticed. At this point there is a marked hyperplasia of the lymphoid elements of the mucosa and submucosa and on the side to which the mesentery is attached the peritoneal, muscular and submucous layers are infiltrated with a carcinomatous growth similar to that in the ovary, while here and there in the muscular coats generally are small islands of carcinoma cells sometimes contained in vessels, but whether lymph channels or veins is not determined. A few light adhesions are attached to the surface of the appendix, and in one of these there is a small nest of carcinoma cells. The mesenteriolum is also invaded by the growth chiefly in its outer half.

In this case it is probable that the carcinoma cells were carried through the peritoneal lymph spaces to the mesenteriolum and thereupon invaded the various coats of the appendix. This view is maintained by the occurrence of the few superficial nodules distributed over the peritoneum which are probably metastatic, as the main tumor is enveloped in a smooth fibrous capsule and not apt to give rise to implantation growths, and from the fact that the principal focus of invasion is at a point contiguous to the mesentery, which is also extensively involved in its corresponding portion.

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A CASE OF TRANSIENT SPASTIC CONVERGENT STRABISMUS.

By Samuel Theobald, M. D.,

Clinical Professor of Ophthalmology and Otology, Johns Hopkins University; Ophthalmic and Aural Surgeon to The Johns Hopkins Hospital, Baltimore.

Spastic convergent strabismus, or strabismus from tonic spasm of the internal recti muscles, a condition to be sharply differentiated from ordinary concomitant convergent squint and from squint due to paralysis of the abducens, is one of the well-recognized ocular manifestations of hysteria; but, apart from this, it would seem, deserves to be regarded as a rare anomaly, to which, as a rule, the text-books upon diseases of the eye devote but scant attention.

De Schweinitz, in the paragraph of less than five lines which he devotes to "spastic strabismus," † says that it "occurs only under rare circumstances in hysteria and brain disease (meningitis). It is difficult of diagnosis, periodical concomitant squint in hypermetropia being sometimes inaccurately described as due to spasm of the internal rectus (Mauthner)." Jackson, in a paragraph of equal brevity, says "deviations of the eyes due to spasm of the ocular muscles attend hysterical seizures and some forms of brain-disease. They may assist in the general diagnosis, but have little localizing value, and require no treatment apart from that of their cause." *

Fuchs, though he states that "tonic spasms of the ocular muscles are extremely rare," adds that "many cases of intermittent strabismus belong under this head," and he mentions two cases of this character which he had observed in

* A paper read before the American Ophthalmological Society, May 3, 1900.

† Diseases of the Eye, third edition, p. 554.

* Diseases of the Eye, p. 234.

hysterical women.* Roosa says children, in whom optic neuritis is found to be present, are often brought to ophthalmic clinics with strabismus in its early stages which is non-paralytic. "Every careful observer," he adds, "will take great pains to determine in a given case of suddenly occurring strabismus, that there is not some cerebral lesion. During dentition, certain children are apt to squint." This, he thinks, "may fairly be ascribed to cerebral irritation." † Duane, in his chapter upon "movements of the eyeballs and their anomalies," in De Schweinitz and Randall's American Text-Book of Diseases of the Eye, Ear, Throat and Nose (p. 511), treating of paretic and spastic squint, says "spasm, which is much less frequent than paralysis, is due to irritative lesions (meningitis, etc.), chorea, epilepsy, and hysteria; rarely is idiopathic." Noyes, Norris and Oliver, Fick, Nettleship and Swanzy, so far as revealed by a glance through their respective treatises upon diseases of the eye, make no mention of the subject of spastic strabismus.

In Norris and Oliver's System of Diseases of the Eye, Parinaud, treating of the ocular manifestations of hysteria, considers at some length the "anomalies of convergence" occurring in this condition. If we would understand the anomalies of the movements of the eyes in hysteria, we must, he says, "consider that neither muscles nor nerves, but nerve centers, and, indeed, the higher centers, are affected—those whereby the movements themselves are brought into unison with psychic action"; and, he adds, "another fact connected with a study of hysterical disorders of the ocular apparatus is that they are almost always of the nature of contractures, even when they present the objective characteristics of paralysis." ‡ In the same volume (pp. 708 and 710), Santos-Fernandez, writing of the "ocular manifestations in influenza," mentions cases of paralysis of the third and sixth nerves and of "convergent strabismus" as having been observed in this affection, while Culver, in the chapter upon "Anomalies of the motor apparatus of the Eye," says "Changes in the centers of innervation as *primary* causes of strabismus are admissible only in certain definite cases," and, again, "Convergent strabismus may be due also to a *spasm of convergence*, independently of accommodation and refraction. We have observed cases of this kind in hysteria. It is perfectly admissible that the same phenomenon is produced in consequence of other irritations of the center of convergence." §

Briefly described, the case which I wish to report is as follows:

A little girl, seven years of age, convalescing from a pronounced attack of influenza, a marked feature of which had been persistent and severe headache, and during the course of which an otitis media had developed in the right ear, complained of diplopia, and on the following day exhibited an evident squint. At the request of the attending physician, Dr. W. D. Booker, I saw the case on the second or third day after the squint manifested itself.

There was present at this time, in both distant and near vision, a very decided convergent squint of the left eye. There were no signs of paresis of either rectus externus—each eye could be rotated outward farther than is commonly possible, and neither the extent of the squint nor the diplopia was influenced by the direction in which the head or the eyes were turned. The pupils were of normal size and there were no signs of either paralysis or spasm of the ciliary muscles. The ophthalmoscope revealed a hypermetropia of rather more than 2 D., and, as I had previously performed a tenotomy upon the little patient's mother for a pronounced esophoria, I concluded that the influenza had been the straw which had broken the camel's back, and developed a concomitant squint in a child who had, probably, inherited insufficiency of the external recti muscles and who was decidedly hypermetropic. That the trouble would be overcome without glasses or an operation seemed to me highly improbable. Dr. Booker had already prescribed iron and quinine and a nourishing diet, and the general condition of the patient was improving from day to day.

At my second visit, four days later, although the mother reported that the eyes had been straight at times during this interval (?), I found the squint unchanged except that it showed, perhaps, a greater tendency to alternate. Thinking that suppression of the accommodation might favorably influence the squint, I directed a two-grain solution of atropia to be dropped into the eyes twice a day. Two days subsequently, the eyes being thoroughly under the influence of the atropia, the squint seemed somewhat less marked. My next visit was five days after this, and, to my gratification, I then found no trace of the squint remaining. Not only so, but even with the cover test it showed no disposition to recur, and an esophoria for distance of only four degrees was shown by the Maddox rod. A decided change for the better in the general condition of the patient was also evident.

After another interval of four days, the eyes meantime having remained quite straight, the atropia was discontinued, although, I confess, I still had serious misgivings as to what would occur when the ciliary muscles began to regain their activity. However, my apprehension proved to be groundless, for a week elapsed without any recurrence of the squint, by which time she had recovered her power of accommodation sufficiently to be able to read ordinary print. The Maddox rod now showed an esophoria for distance of only 3°, while, more noteworthy still, the vertical diplopia test showed at 12″ a so-called exophoria of 4°—a practically normal muscle balance. Since then the eyes have given no further trouble.

A few days since (April 26th), nearly two months having elapsed since the disappearance of the squint, the muscle balance was tested with the following result:

Esophoria $20' = 1°$ } Rod test.
No hyperphoria $20'$ }
Exophoria $12'' = 1°$ (Vertical diplopia test).

* Text-Book of Ophthalmology, p. 576.
† Diseases of the Eye, p. 553.
‡ Vol. IV, p. 754.
§ Op. cit., p. 100.

That the squint in this case was a purely spastic one, due, doubtless, to an irritation (of influenzal origin) of the innervation center which controls the associated action of the internal recti muscles, is, in my judgment, not open to question. Had it been a concomitant squint, precipitated by the attack of influenza, as I at first supposed, it might, indeed, have disappeared under the influence of the atropia and with the improvement in the patient's general condition; but, under such circumstances, a normal muscle balance would certainly not have been reëstablished in the space of a few days, as actually happened. On the contrary, a marked, and probably persistent, esophoria would certainly have been encountered.

As to abductor paresis, I have already said there were no signs whatever pointing in this direction; but, apart from this fact, the rapid return of the lateral muscles to a condition of practical orthophoria, is as little consistent with this view of the case as it is with the view that the squint was a concomitant one.

An incomplete search through the literature of the subject has revealed only one case which bears a close resemblance to my own. In the Archives of Pediatrics, Vol. 1, p. 634, Dr. Samuel S. Adams, of Washington, reports an interesting case of convergent strabismus as a sequela of diphtheria, in which paresis of the external recti muscles was excluded, and which he attributed to "a spasm or over-action of the internal rectus" due to an irritation of the center of ocular adduction. The squint disappeared completely within a few days of its onset.

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NOTES ON NEW BOOKS.

Surgical Pathology and Therapeutics. By JOHN COLLINS WARREN, M. D., LL. D., Professor of Surgery in Harvard University; Surgeon to the Massachusetts General Hospital. Second edition. (*Philadelphia: W. B. Saunders*, 1900.)

The writings and reputation of the author of this much-needed book are sufficient to warrant a scientific, practical and very useful work on surgical pathology. His physiological and pathological knowledge combined with his great experience in teaching are evident throughout the book. These make it not only a valuable text-book but also a reference-book because of the thoughtful combination of physiological and pathological knowledge with a fairly extensive use of historical and biographical references. There is a great present need of this book, which will be a guide to workers and a model on which future writers may build—adding here and there a few innovations in methods, if not in materials.

The new edition differs from the first one only in the addition of a more extensive appendix which is designed to act as a clinical guide in working up surgical cases. It also contains what is not commonly found in surgical works—an article which may bring it into the hands of the dental surgeon. This is a very useful section on the bacteriology of the mouth and how to prepare for filling teeth.

Bacteriology may be considered completely treated when we add to the detailed work on bacteriological technique and surgical bacteria of the main body of the book, the appended bacteriology of the skin, pleura, joints, bladder, eye, ear and nose, and a paragraph on bacteriological examinations.

Omissions made in the original are supplied in the appendix. It was a notable oversight in the first edition not to speak of one of the most important of the surgical bacteria, the Bacillus Aerogenes Capsulatus (Welch), and the omission of the Gonococcus as a cause of peritonitis. This has been rectified in the appendix and the Pneumococcus and Typhoid bacillus are given more scope as surgical bacteria.

A valuable introduction to the article on inflammation is given in Chap. III on Hyperæmia in which the relationship between physiology and pathology is clearly brought out.

The chapter on inflammation is a type of the work, being eminently practical and scientific. The references to works on the subject are full but not too extensive.

It is worthy of note that after reviewing so usefully and thoroughly the writings of those most worthy of quotation the author ends his chapters with his own healthy view of the subject.

Infective inflammation is dealt with in three chapters. This differs from the simple form in that it is due to bacteria and spreads, usually ending in suppuration. The etiology is included with some practical points on invasion of tissues. Under the same head comes Acute Osteomyelitis with a very useful, complete description of the local action of the infective process. The various causative agents and their differences in action with the change in the part acted on are noteworthy. Repair is sharply separated from inflammation, as it should be. The nervous theory of shock gets greatest credit after a historical review of the subject.

In five chapters the author gives a clear portrayal of the fevers of surgery, the physiological basis preceding the pathological condition being first described. Traumatic, Aseptic and Urethral Fevers, Septicæmia, Pyæmia and Erysipelas come under this head. Tetanus is thoroughly treated of in a special chapter; its bacteriology and treatment by antitoxins being described in other chapters.

Tuberculosis of bone is well handled—the manifold pathological appearances and clinical pictures being given in a concise, yet complete manner. The experimental work stands forth promiently—Cheyne and Krause getting credit for much good work.

Under tuberculosis of joints Warren very properly adheres to Cheyne's view that there are two forms, one beginning in the joint, another being primary in the bone. In the treatment of abscesses the healing power of iodoform is asserted.

Chapter XXVI deals with tuberculosis of the soft parts, including the peritoneum, glands and genito-urinary tract. Diseases of bone have a special chapter and include all of the diseases not dealt with under the headings Osteomyelitis, Tuberculosis, and Tumors of Bone—there are many of them. Osteopsathyrosis, Senile Atrophy and Osteoporosis are said to denote closely allied conditions of bone, the absorption of the bone being due to "lacunar absorption." Neuroparalytic Atrophy, that due to the pressure of aneurisms and to malignant growths, is included under the heading Osteoporosis. Nearly all known diseases of bone are included in this chapter.

It is remarkable how the author has managed to include all the practical points of surgical pathology in some way, leaving out no important ones. If not found in their natural places they turn up somewhere else.

There is nothing of special note in the chapter on Tumors. The classification is the simplest possible. Endothelioma is classed with Carcinoma; yet, when writing about Sarcoma, it is shown how the endothelial tumors are closely related to them. The theories of tumor-formation are discussed, especially the parasitic theory, which still remains not proven.

In describing Sarcoma and Carcinoma each organ and locality of the body is taken up in order, with its peculiar tumor growths. The use of the Mixter punch in settling the question of malignancy of a new growth might be criticised.

Besides the surgical treatment of Carcinoma the author is not sure but that something may develop from the work on the injections of cancroin—extracted from cancer cells as recommended by Adamkiewicz.

A few drawings of macro- and micro-scopic aspects of tumors are given but no special merit is noted in the illustrations.

The appendix has been written to fill in what did not fit well in the main body of the book and to give the special bacteriology of various localities and organs.

It is well that it was added, if for no other reason than the addition of a useful article on peritonitis. The old edition only alludes to peritonitis of tubercular origin.

Here too are added certain good points on pathological technique and clinical microscopy and corrections are made of oversights in the main body of the book. Subjects not usually treated of in surgical text-books are here brought forward.

In the chapter on Scientific Aids to Surgical Diagnosis, which is a rather overcrowded article, after insisting that the surgeon should know enough of laboratory methods to be able to say which of them can give him positive results in case a specimen is sent for examination, he refers to some things to be learned from blood-examinations; gives some points in bacteriological technique, and speaks of the necessity for animal inoculation. In this chapter a great number of bacteriological data, urinary symptoms and findings are crowded together in marked contrast to the clearer writing of the original edition.

To the Röntgen rays is devoted a special article describing their value in detecting fractures, foreign bodies, calculi, etc. Their advantages and disadvantages are referred to, and several illustrations are added.

Chapter II deals with the surgical bacteriology of the skin, and treats of wound-infection and disinfectants in a brief and practical manner. Useful points in technique, such as the preparation of ligatures, of the patient, of instruments, of the surgeon, and the treatment of the wound, not included in the original are found here. Serum therapy is also dealt with in its relation to tuberculosis, tetanus, syphilis and streptococcus infections.

The contents of the whole volume are of the greatest value, and the matter is presented in a very interesting manner by one who is a master and teacher.

The Medical Annual and Practitioner's Index, 1900. (*J. Wright & Co., Bristol, and E. B. Treat & Co., New York.*)

The present number, the eighteenth of its publication, is well up to the standard of previous years. In recently noting the Synoptical Index of this work for the years 1887-1898 we commented on its valuable features. The extracts and notes of articles are usually well made, some of them giving the important points more clearly than they are given in the original articles. Special attention may be drawn to the section on Malarial Fever, by Major Ronald Ross. It gives an excellent short account of the recent work on that subject. Colonel Keith Hatch contributes an interesting article on Mycetoma which is well illustrated. To those who have used the Annual its good points are well known. It may be recommended to those who do not know it as being helpful in many ways.

Pye's Surgical Handicraft. Fourth edition, revised and enlarged, by Bertram Rogers, M. D. (*John Wright & Co., Bristol*, 1900.)

It is a pleasure to see another edition of this work, eight years having elapsed since the third edition. It was first published by the late Mr. Pye, in 1884, and some words of his original preface regarding the title of the work may be quoted: "Although surgery is doubtless becoming more scientific day by day, nevertheless it will never cease to be a skilled labor nor will surgeons ever cease to be handicraftsmen." His object in the book was to describe the details of surgical work from the point of view of house surgeons and "dressers" in the surgical wards. With this purpose the work is thoroughly practical and the descriptions are plain and accurate. At the time when one is first battling with the many difficulties and emergencies that come to the young house officer, this book is a great help. There are few surgical conditions that are not described and the advice given is usually sound. Every senior student and young graduate will find this work useful. We speak with grateful remembrance of its assistance in days gone by when one dwelt with the fear of an improperly treated emergency ever before his eyes.

Injuries to the Eye in their Medico-Legal Aspect, by S. Baudry, M. D., Professor in the Faculty of Medicine, University of Lille, France; translated from the original by Alfred James Ostheimer, Jr., M. D., of Philadelphia, Pa.; revised and edited by Charles A. Oliver, A. M., M. D., Attending Surgeon to the Wills Eye Hospital, Ophthalmic Surgeon to the Philadelphia Hospital, Member of the American and French Ophthalmological Societies, etc., With an Adaptation of the Medico-Legal Chapter to the Courts of the United States of America, by Charles Sinkler, Esq., Member of the Philadelphia Bar. (*Philadelphia, New York, Chicago: The F. A. Davis Company, Publishers*, 1900, pp. X-161. Price $1.)

It is not long since that we had the pleasure of perusing another of Prof. Baudry's contributions, "Simulated Blindness" in The System of Diseases of the Eye, by Norris and Oliver (Vol. IV), and perhaps the Lille professor is best known to many of his American readers as one of the contributors to that standard work on ophthalmology.

American ophthalmologists seem to be less familiar nowadays than formerly with what is going on in the domain of French ophthalmology, a condition of affairs which is to be attributed to the fact that in this branch of medicine more than ever before inspiration is being drawn from Germany. We should not forget, however, what de Wecker, Panas, Landolt and Meyer have done and that they are still working at the very front.

The object of Professor Baudry's work is to equip the ophthalmologist with a medico-legal knowledge of injuries to the eye. It is surprising that ophthalmic literature is so poor in information of this character. The author has collected his personal observations and compiled the reports and published conclusions of others upon this subject. It is a short work consisting of scarcely one hundred and fifty pages and is full of practical information. The contents will not strike one as being something which is entirely new, for the clinical facts, at least, with which every page is full, are all old stories and form part of the mental equipment of every experienced ophthalmologist. The book will be useful, however, because it contains these clinical facts condensed and so arranged as to form what may be regarded as a distinct and important chapter in ophthalmology, "Eye Injuries." It is needless to say that such a presentation of the subject leaves a clear impression.

In its application to the legal status or value of an injury to the eye it is to be hoped that the work will be found useful, though we doubt whether it can be regarded as a preeminently valuable guide to the expert in estimating accurately the damage caused by the injury to the individual. Such a work we think ought to contain more clinical records with the legal points to which they give rise, and should be illustrated by pertinent cases with their legal conclusions or decisions.

It is divided into four parts: 1. "Traumatic Lesions of the Ocular Adnexa." 2. "Traumatic Lesions of the Eyeballs." 3. "Simulated or Exaggerated Affections of the Eye." 4. "Medico-Legal Expert Testimony."

We look upon Part Third, which treats of a theme on which Baudry is a recognized authority, as the best in the book; that is, from a medico-legal point of view. Professor Jacquey, of Lille, has contributed the legal portion of the last chapter, which is to the point and is an epitome of the principles which govern opinion-evidence and will be found to contain what every practitioner of medicine should know.

In conclusion we are happy to bear witness to the readableness of Doctor Ostheimer's translation and to this further token of the industry of Doctor Oliver, the editor.

R. L. R.

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In the methods of instruction especial emphasis is laid upon practical work in the Laboratories and in the Dispensary and Wards of the Hospital. While the aim of the School is primarily to train practitioners of medicine and surgery, it is recognized that the medical art should rest upon a suitable preliminary education and upon thorough training in the medical sciences. The first two years of the course are devoted mainly to practical work, combined with demonstrations, recitations and, when deemed necessary, lectures, in the Laboratories of Anatomy, Physiology, Physiological Chemistry, Pharmacology and Toxicology, Pathology and Bacteriology. During the last two years the student is given abundant opportunity for the personal study of cases of disease, his time being spent largely in the Hospital Wards and Dispensary and in the Clinical Laboratories. Especially advantageous for thorough clinical training are the arrangements by which the students, divided into groups, engage in practical work in the Dispensary, and throughout the fourth year serve as clinical clerks and surgical dressers in the wards of the Hospital.

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As candidates for the degree of Doctor of Medicine the school receives:

1. Those who have satisfactorily completed the Chemical-Biological course which leads to the A. B. degree in this university.

2. Graduates of approved colleges or scientific schools who can furnish evidence: (a) That they have acquaintance with Latin and a good reading knowledge of French and German; (b) That they have such knowledge of physics, chemistry, and biology as is imparted by the regular minor courses given in these subjects in this university.

The phrase "a minor course," as here employed, means a course that requires a year for its completion. In physics, four class-room exercises and three hours a week in the laboratory are required; in chemistry and biology, four class-room exercises and five hours a week in the laboratory in each subject.

3. Those who give evidence by examination that they possess the general education implied by a degree in arts or in science from an approved college or scientific school, and the knowledge of French, German, Latin, physics, chemistry, and biology above indicated.

Applicants for admission will receive blanks to be filled out relating to their previous courses of study.

They are required to furnish certificates from officers of the college or scientific schools where they have studied, as to the courses pursued in physics, chemistry and biology. If such certificates are satisfactory, no examination in these subjects will be required from those who possess a degree in arts or science from an approved college or scientific school.

Candidates who have not received a degree in arts or in science from an approved college or scientific school will be required (1) to pass, at the beginning of the session in October, the matriculation examination for admission to the collegiate department of the Johns Hopkins University, (2) then to pass examinations equivalent to those taken by students completing the Chemical-Biological course which leads to the A. B. degree in this University, and (3) to furnish satisfactory certificates that they have had the requisite laboratory training as specified above. It is expected that only in very rare instances will applicants who do not possess a degree in arts or science be able to meet these requirements for admission.

Hearers and special workers, not candidates for a degree, will be received at the discretion of the Faculty.

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Since the opening of the Johns Hopkins Hospital in 1889, courses of instruction have been offered to graduates in medicine. The attendance upon these courses has steadily increased with each succeeding year and indicates gratifying appreciation of the special advantages here afforded. With the completed organization of the Medical School, it was found necessary to give the courses intended especially for physicians at a later period of the academic year than that hitherto selected. It is, however, believed that the period now chosen for this purpose is more convenient for the majority of those desiring to take the courses than the former one. The special courses of instruction for graduates in medicine are now given annually during the months of May and June. During April there is a preliminary course in Normal Histology. These courses are in Pathology, Bacteriology, Clinical Microscopy, General Medicine, Surgery, Gynecology, Dermatology, Diseases of Children, Diseases of the Nervous System, Genito-Urinary Diseases, Laryngology and Rhinology, and Ophthalmology and Otology. The instruction is intended to meet the requirements of practitioners of medicine, and is almost wholly of a practical character. It includes laboratory courses, demonstrations, bedside teaching, and clinical instruction in the wards, dispensary, amphitheatre, and operating-rooms of the Hospital. These courses are open to those who have taken a medical degree and who give evidence satisfactory to the several instructors that they are prepared to profit by the opportunities here offered. The number of students who can be accommodated in some of the practical courses is necessarily limited. For these the places are assigned according to the date of application.

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